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THE TREATMENT OF AMENORRHEA WITH LARGE DOSES OF ESTROGENIC HORMONE

RAPHAEL KURZROK, PH.D., M.D., LEO WILSON, M.D., AND MICHAEL A. CASSIDY, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, and the Sloane Hospital for Women, the College of Physicians and Surgeons, Columbia University)

THE number of hormones immediately concerned with menstruation has recently been recognized to be four: the follicle stimulating hormone (prolan A), the luteinizing hormone (prolan B), both originating from the anterior pituitary gland; the follicular hormone* (estrin), and the corpus luteum hormone (progestin or corporin) originating in the ovary. Regarding the quantitative requirement of these hormones nothing was definitely known until the recent work of Kaufmann (1932, 1933), which was confirmed by Loeser (1932), Clauberg (1933), and Buschbeck (1934). Werner and Collier (1933) reported the growth of the endometrium in recently castrated patients by means of theelin. Kaufmann concluded that 40,000 to 50,000 R.U. of estrin were necessary to reproduce the entire proliferative (postmenstrual) phase of the endometrial cycle. If this was immediately followed by 35 to 50 rabbit units of corpus luteum hormone,† a pregravid or secretory endometrium would then result, and thereupon typical menstruation would follow. By typical menstruation we imply bleeding from a pregravid or secretory

*Also known as amniotin, female sex hormone, progynon, theelin, etc.

†There are 2 types of units used for corpus luteum hormone, namely, the Allen-Corner and the Clauberg. The Allen-Corner unit is about four times as large as the Clauberg unit.

endometrium. This is to differentiate it from cyclical bleeding where we imply bleeding from a built up proliferative endometrium. Evidence is beginning to accumulate that in the normal woman there may exist both types of bleeding, corresponding to the ovulatory and anovulatory cycle in the Macacus rhesus monkey (Hartman, 1932). Hisaw and Leonard (1930) have shown that before corpus luteum hormone can act upon the endometrium, the latter must first be built up by estrin to the proliferative phase. Smith and Engle (1932) have demonstrated that both estrin and progestin, acting upon the endometrium one after another, and in proper dosage, are necessary to produce typical menstruation in the castrated monkey. Cyclical bleeding may be produced by estrin alone in the monkey (Smith and Engle, 1932) and in the human being (Kaufmann, 1932, and others). This bleeding occurs from a proliferative type of endometrium and is accompanied by a moderate destruction of tissue. We have produced this form of cyclical bleeding in a group of patients with primary and secondary amenorrhea. Patients who have had periods cannot distinguish such cyclical bleeding from typical spontaneous menstruation.

The estrogenic substances used in our cases were amniotin* and the benzoic acid ester of dihydroestrin (progynon B). The solvent for both is oil. The concentration of hormone is as follows:

Amniotin 1 c.c. = 1,000 R.U. (5,000 M.U.)
Progynon B. 1 c.c. = 10,000 R.U. (50,000 M.U.)

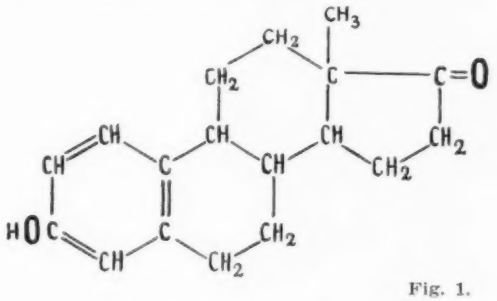
The two substances are not identical chemically. Amniotin is derived from the amniotic fluid of cattle and is chemically a ketohydroxyestrin (Fig. 1). Progynon B is derived from mares' urine first as ketohydroxyestrin. In an important experiment Schwenk and Hildebrandt (1933) found that by reducing the keto group (=C=O) to a hydroxyl group (significant groups noted by circles), so as to form dihydroestrin (Fig. 3), the estrogenic activity of the hormone is "stepped up" tremendously. Because of the protracted excretion of the benzoic ester of estrin, first observed by Butenandt (1931), a benzoic acid ester of the dihydroestrin was prepared by coupling the phenolic hydroxyl (on ring A) with benzoic acid (Fig. 4). The esterification of the dihydroestrin reduces its activity but prolongs its physiologic effect,† because the ester is more slowly broken up by the body. As the dihydroestrin and its esters are much more soluble in oil than estrin itself, the use of these com-

*We are exceedingly grateful to E. R. Squibb & Sons, for their supply of amniotin, and to the Schering Corporation for their supply of progynon B. We are also indebted to Dr. Erwin Schwenk for his many helpful suggestions relating to the chemistry of these hormones.

†When 1 M.U. of estrin is injected, full estrus is caused for only a day, and diestrus (interval between two estrus cycles) is restored within four days, the injection of 1 M.U. of the benzoate is followed by an estrus lasting for about five days, and complete diestrus is restored in some thirteen days after the injection. The clinical significance of this effect is apparent.

pounds has the further advantage that it is possible to use higher concentrations, thus avoiding the disadvantage of too many injections.

The significance of our understanding the chemical structure of estrin is strikingly manifested by the subsequent facts. By the simple chemical process of reduction (addition of hydrogen) a compound is formed whose activity is greater than the hormone isolated from urine. It might be reasoned that if the addition of one hydroxyl group (to the one already present) markedly enhances the activity of estrin, the addition of two hydroxyl groups should have a still more potent effect. On the contrary, the resultant compound is theelol (trihydroxyestrin) (Fig. 5) whose



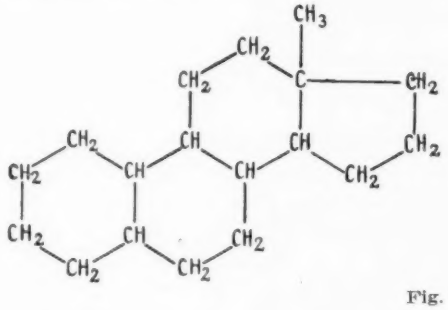
Ketohydroxyestrin* or
estrin or
amniotin or
theelin $C_{18}H_{22}O_2$.
1 gm. = 4,000,000 M.U. or
= 800,000 R.U.†

Fig. 1.

estrogenic activity is much less than estrin. (However, it is more potent than the ketohydroxyestrin if administered by mouth.)

Similarly, continued reduction or hydrogenation of estrin does not yield a more active compound. If the benzene ring (A) is reduced

*The nomenclature of the estrogenic substances has been complicated by the numerous trade and special names and by the large number of isomers that is represented by the same formula. Adam et al. (1933) have suggested a very attractive nomenclature. They have named the fundamental saturated hydrocarbon. "estrane," $C_{18}H_{30}$ which is 2-methyl-1, 2-cyclopentano-perhydrophenanthrene, and have suggested the terms "estrone" for ketohydroxyestrin (estrin, theelin) and "estriol" for trihydroxyestrone (theelol).

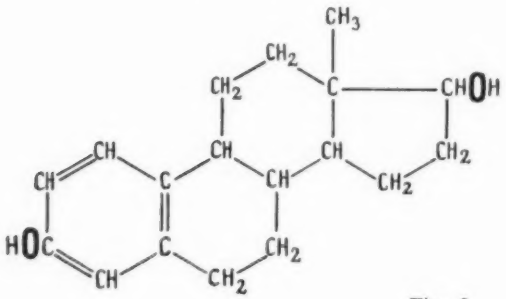


Estrane
$C_{18}H_{30}$

Fig. 2.

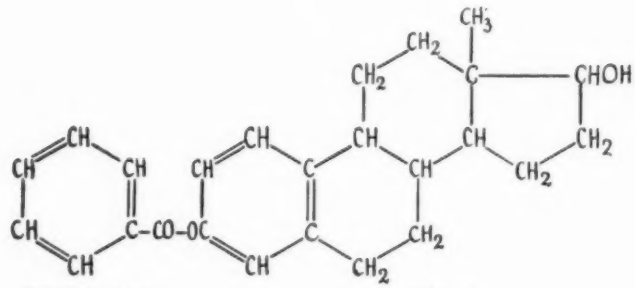
†The exact unit for estrin is still an unsettled problem. The unit depends upon the size, age, condition, and breed of the rat or mouse; the frequency of injection, the solvent for the hormone, the number of animals used, the type of vaginal smear regarded as a positive response, the frequency with which smears are examined and the times selected for examination. For instance, 1 R.U. = 5 to 12 M.U. depending upon the above conditions. To this has recently been added the international unit or the number of mouse units in one gamma (0.001 mg.) of crystalline material. The number of international units in a rat unit varies, according to the different investigators, from 3 to 35, depending possibly on the number and type of isomers in the crystalline material.

completely (Schoeller, Schwenk and Hildebrandt, 1933), the result is a substance which behaves like the testicular hormone from which it, in



Dihydroestrin = $C_{15}H_{24}O_2$
1 gm. = 25,000,000 M.U. or
= 5,000,000 R.U.

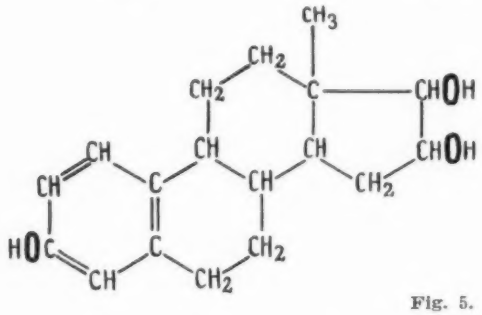
Fig. 3.



Benzoic acid ester of dihydroestrin or progynon – B.
1 gm. = 12,500,000 M.U. or
= 2,500,000 R.U.

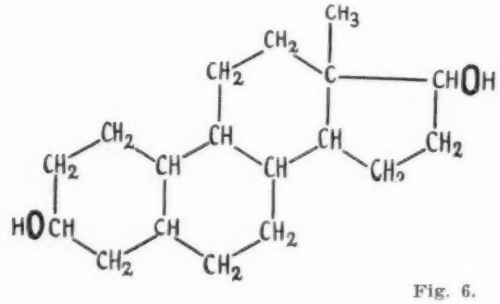
Benzoic Acid

Fig. 4.



Theelol or trihydroxyestrin.
1 gm. = 15,000 – 40,000 R.U.
or
75,000 – 200,000 M.U.

Fig. 5.



Hydrogenation product of estrin.
3,17 dihydroxyestrane

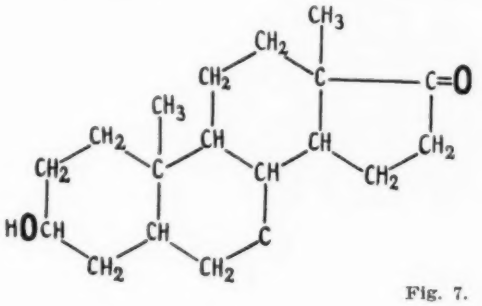
Fig. 6.

fact, differs only by the absence of one $-CH_3$ group and the presence of a hydroxyl group instead of the keto (=CO) group (Fig. 6).

Testicular hormone is in turn closely related to ergosterol (Fig. 7). When ergosterol is irradiated under suitable conditions it becomes antirachitic (similar to vitamin D). Both ergosterol and vitamin D are estrogenic (Dodds, Cook, Hewitt and Lawson, 1933). The intimate relationship between hormones and vitamines is thus illustrated.

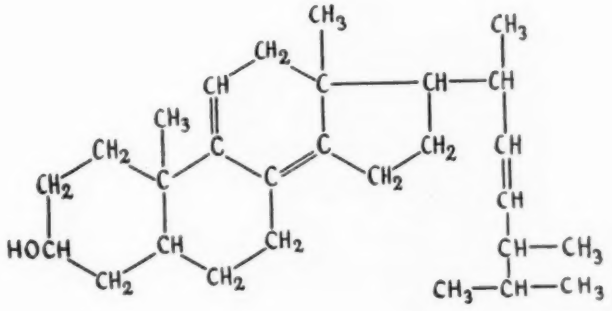
The action of estrin and progynon B are similar; namely:

1. They stimulate the growth of all secondary sex organs; in particular:
   A. The endometrium, to form the proliferative phase of the menstrual cycle.
   B. The myometrium.
   C. The duct system of the breasts.
2. In excessive doses they cause luteinization of ovaries in the rat by way of the anterior pituitary (Hohlweg, 1934). A loss of estrous cycles follows subsequently.



Testicular hormone

Fig. 7.



Ergosterol

Fig. 8.

This by-effect from large doses was also apparent clinically. Several patients with normal menstrual cycles were given 40,000 to 60,000 R.U. of progynon B, and as a result the succeeding menstrual cycle was skipped. After a month or two of amenorrhea normal menstruation recurred. We believed that this amenorrhea was probably due to luteinization of the ovaries. This being the case, we argued that, very large doses might be tried in cases of bleeding from cystic and glandular hyperplasia of the endometrium, with a known failure of luteinization. The results from 40,000 to 100,000 R.U. were merely an increase in the bleeding, for it must be remembered that excessive doses of estrin pro-

duce cystic and glandular hyperplasia of the endometrium (Burch, Williams, and Cunningham, 1931). Whether still greater dosage might have produced the desired luteinizing effect in these cases was left an open question.

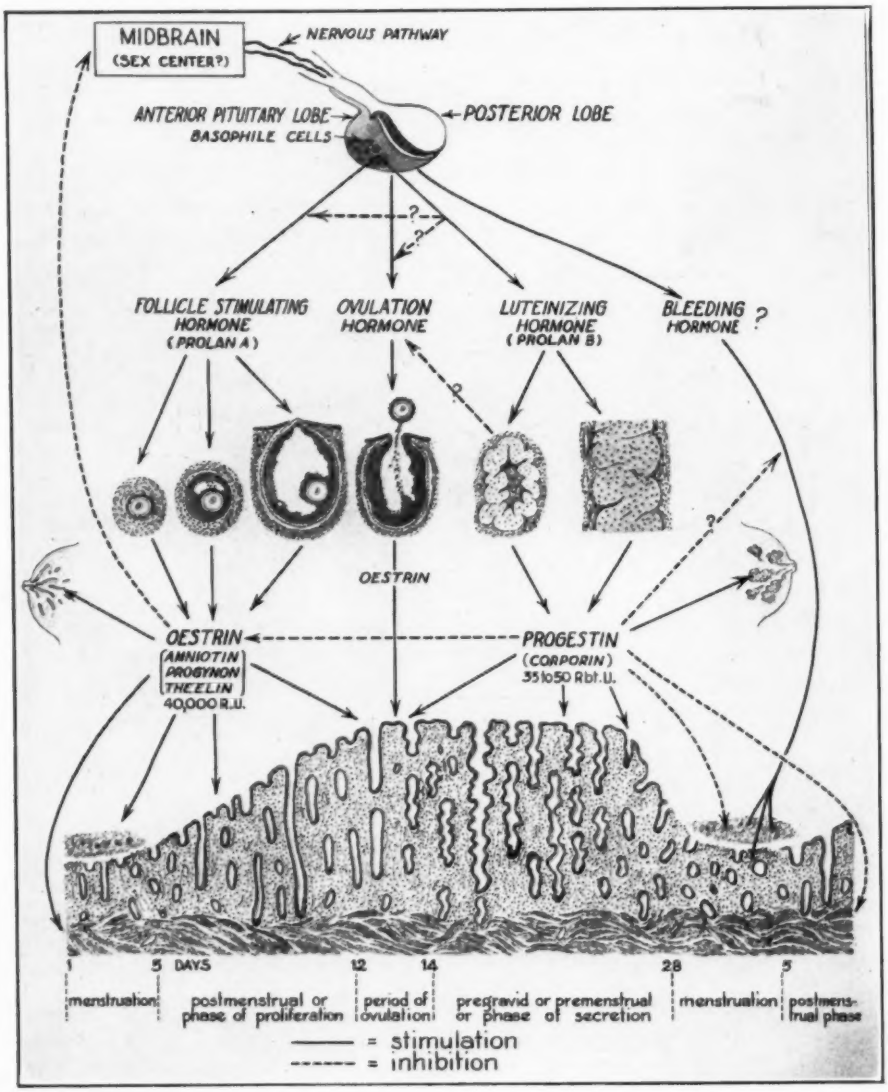


Fig. 9.—Represents the sex hormones involved in the menstrual cycle and their interrelationships. The ovarian hormones are represented quantitatively, the progestin in terms of the Clauberg Unit. A sex center is postulated mainly on the work of Teel and Cushing (1930) and Hohlweg and Junkmann (1933). The relation of the breasts to the ovarian hormones is also shown.

No toxic symptoms were observed from the administration of large doses of estrogenic hormone. While the dosages given appear very great, it must not be forgotten that 50,000 R.U. represent merely 20 mg. of crystalline dihydroestrin benzoate.

PHYSIOLOGY OF MENSTRUATION

Fig. 9, schematically represents our concept of the menstrual cycle. Estrin dominates the first half of the cycle. Under normal conditions, when the endometrium has been completely built up, ovulation occurs and this is followed by the transformation of the ruptured follicle into a corpus luteum. This luteinization is the result of the action of one of the gonadotropic hormones, the luteinizing hormone, upon the ruptured follicle. (Luteinization may also occur without follicle rupture.) In the treated cases of primary amenorrhea where there appears to be no ovarian function, the phase of secretion in the endometrium cannot occur without addition of corpus luteum hormone. On the other hand, cases of primary amenorrhea that present functioning ovaries (where

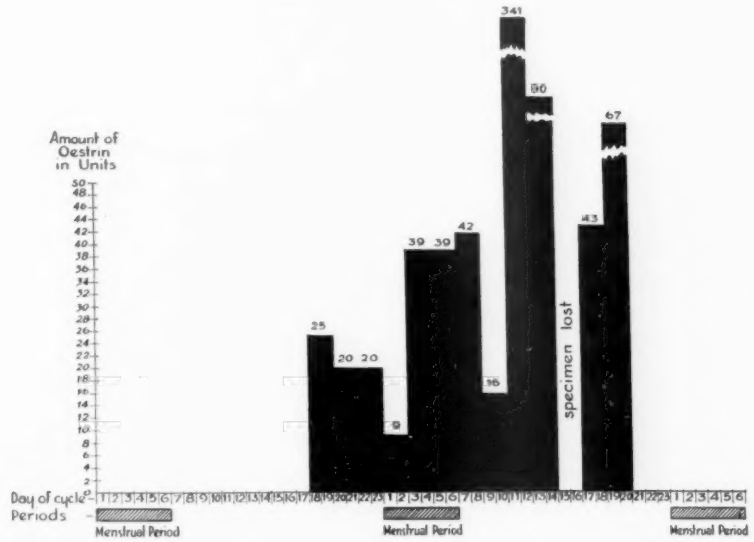


Fig. 10.—Shows the urinary excretion of estrin during an entire menstrual cycle. This patient (twenty-two years of age) presented no gynecologic pathology. Menses regular every twenty-three days, six days in duration, moderate in amount and without discomfort. The entire urinary excretion for two days was pooled and measured, and the hormone determination carried out on one liter and then calculated for the entire amount. The total hormone excreted during the cycle was 751 R.U. It is important to note that: (1) estrin is present throughout the cycle; (2) there is no loss of estrin during menstruation; (3) the peak of estrin excretion occurs at the time of ovulation (pituitary stimulation of the ovary).

the amenorrhea is due to a hypoplasia of the uterus), can produce a secretory type of endometrium by the action of their own corpus luteum. This is even more evident in cases of secondary amenorrhea. Estrin seems to be the "key hormone" that sets the entire process in motion.

The cause of the actual bleeding, both cyclical and menstrual, is not entirely clear. If the ovaries are removed at the middle of the intermenstrum, or the corpus luteum alone is removed at a little later date, bleeding occurs. Similarly, bleeding occurs a few days after a period of estrin administration, accompanied by degeneration of the endo-

metrium. The usual explanation offered, that the bleeding was caused by the withdrawal of estrin, is not satisfactory in view of the following facts: Werner and Collier (1933) injected patients with large doses of theelin and noted uterine hemorrhage during the period of treatment. Engle (1932) and Hisaw (1933) injected monkeys with gonadotropic extracts and noted bleeding during treatment. Estrin was produced in the animals, for follicles formed in the ovaries, and there was swelling and redness of the sexual skin. Furthermore, there is no withdrawal of estrin at the time of menstruation, as can be seen from Fig. 10, which shows the estrin excretion during a normal menstrual cycle (Creelman and Kurzrok, 1934). Hartman, Firor, and Geiling (1930) made the interesting suggestion that menstruation is not merely a passive process but is due to a specific hormone from the anterior pituitary acting directly upon the uterus. They showed that the bleeding which follows the injection of estrin does not occur in the hypophysectomized monkey. On the contrary, the injection of gonadotropic extracts into the hypophysectomized monkey during the estrin administration caused bleeding from an interval endometrium. In support of this theory Kurzrok, Kirkman and Creelman (1934) have noticed the sudden excretion of the follicle-stimulating hormone during the first day of the period, thus denoting pituitary activity.

In the treatment of our cases we administered the progynon B and the amniotin in a manner so as to simulate as closely as possible the position of the hormone in the cycle. Two injections of hormone of 10,000 R.U.* each were given during the first week, the injections being separated by an interval of three days. During the following week an additional 20,000 R.U. were given, the idea being to give 40,000 R.U. within two weeks. No treatment was administered during the third and fourth weeks. If a period occurred, treatment was begun again immediately after its completion. If a period did not occur the series of injections was started anew. All injections were given intramuscularly in the buttocks. Neither local nor general reactions were ever observed.

The development of the mammary gland and its cyclical changes during menstruation depend upon the hormones produced by the ovary and the anterior lobe of the pituitary. Estrin stimulates the growth of the duct system (Turner, etc., 1932). Corpus luteum hormone stimulates the alveolar apparatus. The breast undergoes cyclical changes during the menstrual cycle. Grueter and Stricker (1929) showed that injections of anterior pituitary extracts into ovariectomized rabbits produced development of the mammary gland and lactation. They believed that previous corpus luteum activity was essential for this growth. Corner (1930) showed that anterior pituitary extracts alone were sufficient to produce mammary growth. Only estrogenic substances were used in our cases.

*When large dosage was required progynon B alone was given. When doses of 1,000 to 3,000 R.U. were necessary, amniotin was given.

The growth of the breasts in the cases of primary amenorrhea where breast development was markedly retarded was very startling. The breast as it grew assumed a pointed appearance with the areoli projecting forward as a distinct convexity. There was growth of the nipple. Where the breasts were already well developed no further growth occurred irrespective of the dosage administered.

It may be stated that in general, a hormone does not directly stimulate the gland that produces it. Hence we did not expect ovarian stimulation from our estrin medication. We merely substituted for one of the hormones of the ovary. On the other hand, secondary effects may be produced in the ovary by way of the anterior pituitary as was done by Hohlweg (1934). This is one of the aims in the treatment of secondary amenorrhea. It is expected that the completion of the proliferative phase will release the mechanism involved in the second half of the cycle, namely, luteinizing and corpus luteum hormones. Another important consideration is that the mere presence of the hormone and the end-organ upon which it acts is not sufficient for physiologic activity. The end-organ must be *responsive* to the hormone available. This is precisely the point in cases of genital hypoplasia. Kurzrok and Ratner (1932) have pointed out that the estrin excretion in many cases of genital hypoplasia is quantitatively the same as in normal women.

Genital hypoplasia was found to be the most common cause of secondary amenorrhea. Why then, did these uteri not respond to the estrin already present in the system? Apparently we are dealing with an inherent defect in the müllerian duct system. Normal stimulation fails to produce a response, but excessive stimulation does produce uterine growth and bleeding. It is necessary to build up these uteri to within normal limits by means of large doses of estrin before they begin to respond again to the estrin supply of their own ovaries.

CASE REPORTS

A. *Primary Amenorrhea.*—We have administered large doses of estrogenic hormone to 12 patients with primary amenorrhea ranging in age from seventeen to forty-three years. On the basis of both physical and hormonal findings these cases fell into two groups:

Group I. Absence of ovarian function.

Group II. Müllerian duct defect; plus presence of ovarian function.

No patient had obesity or hirsutism. The basal metabolism was inconstant and ranged from minus 27 per cent to plus 25 per cent.

TABLE 1. PRIMARY AMENORRHEA

GROUP	UTERUS	VAGINA	BREASTS	ESTRIN	F.S.H.*
I 6 patients	Rudimentary	Rudimentary	Rudimentary	–	+
II a 2 patients	Absent	Absent	Normal size	±	–
II b 4 patients	Infantile	Present but hypoplastic	+ Normal size	±	–

*F.S.H., follicle-stimulating hormone.

Group I (absence of ovarian function) consisted of 6 patients in whom the secondary sex characteristics had failed to develop. The breasts, labia, vagina, and uterus were rudimentary. Roentgenograms of the pelvis (taken in 3 cases) revealed the *android* or male type (Caldwell and Moloy, 1933). Hormone determinations of the urine demonstrated the presence of prolan A in all six cases and the absence of estrin in all but one patient, who on a single occasion excreted 4 R.U. per liter. The repeated finding in the urine of a positive prolan and negative estrin is indicative of absence of ovarian function. Libido was absent. Interest in sex matters was either absent or infantile. When estrogenic hormone was administered, the earliest change noted was the growth of the breasts, which became firm and pain-

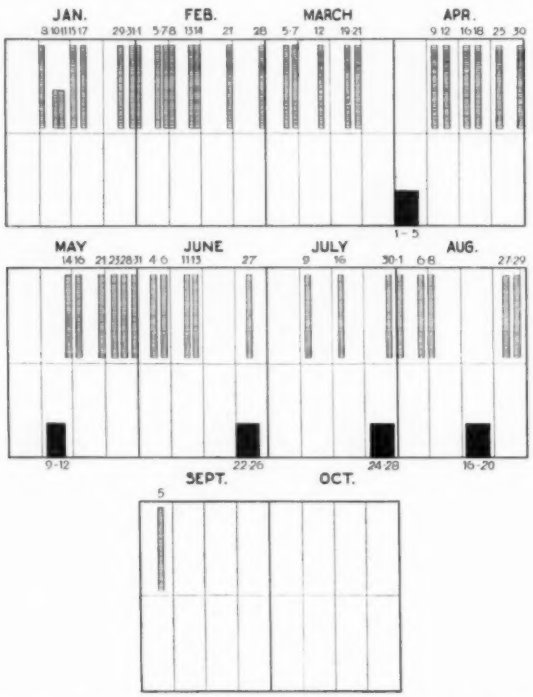


Fig. 11.—L. L. B., aged twenty-two years. Primary amenorrhea. General infantilism. Hypodevelopment of secondary sex characteristics (Group I). Estrin, negative; follicle-stimulating hormone, positive; basal metabolic rate minus 27 per cent 184,000 R.U. of progynon B required to bring on first period. Solid column denotes duration and intensity of flow. Each barred column denotes 10,000 R.U. of estrogenic hormone; shorter columns correspondingly less.

ful. The growth was confined chiefly to the region of the areolae and nipples (duct system). Vaginal secretion was the next to appear accompanied by enlargement of the labia and apparent widening of the vagina. This was soon followed by bleeding from the uterus, which in the beginning showed little if any increase in size. After several months of treatment the uterus became considerably enlarged. The quantity of progynon B and amniotin necessary to produce the above effects varied considerably. In general, it required about 50,000 R.U. to produce appreciable growth of the breasts; 100,000 R.U. to bring about the first period, and about 40,000 R.U. to bring about subsequent periods.

When treatment was stopped, there was no further bleeding. The breasts, labia, and vagina began to atrophy. The myometrium, which was the last to respond to the estrogenic hormone was the last to recede.

Periodic bleeding occurred in all but one patient of this group, the latter having had insufficient treatment. One patient has had 6 periods, two 5 periods, one 4 periods and one a single period (at forty-three years!). The number of periods depended on the duration of the treatment. The flow, which varied from a few hours to several days, was usually scanty in amount but in a few instances was moderate. In no case was the flow profuse. Dysmenorrhea was not a prominent feature. Endometrial biopsies* were not performed because all six patients were virgins.

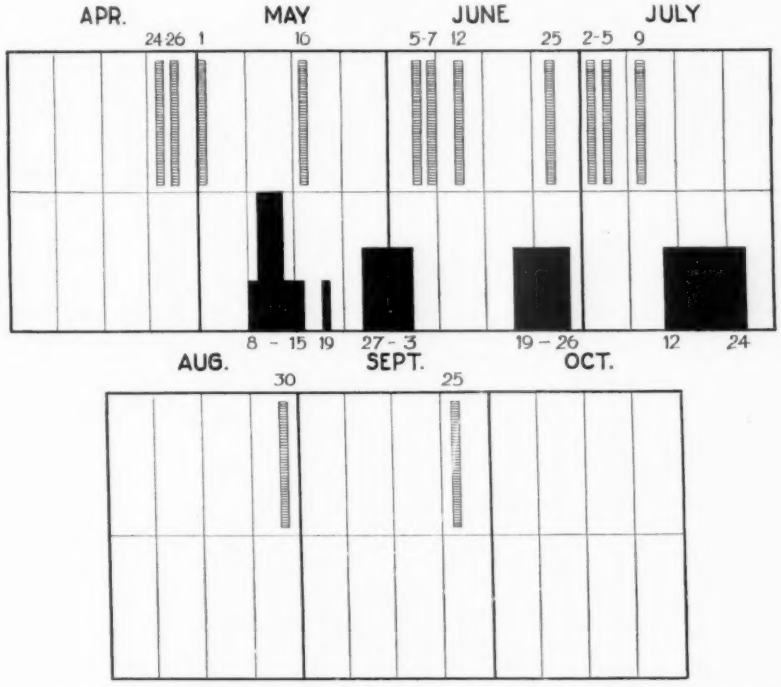


Fig. 12.—H. E., aged twenty-five years. Primary amenorrhea. Married. Normal secondary sex characteristics, infantile uterus (Group II b). 30,000 R.U. of estrogenic hormone were required to bring on the first period. Endometrium removed during the July period showed secretory changes, denoting corpus luteum activity. Treatment reduced in August and September and periods stopped.

Concomitant with the growth of the breasts and the onset of vaginal bleeding, there was a striking mental change in our patients. The development of interest in members of the opposite sex manifested itself in more stylish clothing and the use of cosmetics. (Psychic effect due purely to estrin?)

The second group may be subdivided into two types: (a) total, and (b) partial failure of müllerian duct development. There were two patients of the first type. Their breasts and labia were well developed, but there was complete absence of the vagina and uterus. Hormone determinations of the urine showed no prolan in either

*The biopsy specimens were removed by means of a modified Klinger and Burch (1932) suction curette.

case, but 8 R.U. of estrin was found in one patient and no estrin in the other. The absence of estrin in the latter case does not mean complete cessation of ovarian function; the presence of well-developed breasts and external genitalia and the absence of F.S.H. indicate some ovarian activity.

Each patient was given 100,000 R.U. of progynon B over a period of two months. In one case, there has been definite enlargement of the uterine anlage from a vague thickening in the broad ligament to a nodule the size of a hazelnut. The other case has shown no growth and treatment has been discontinued. The interesting point here is the growth in extrauterine life of an anlage which had previously failed to develop during intrauterine existence.

Group II b (partial failure of müllerian duct development) was composed of four patients. They had infantile uteri but well-developed breasts and external genitalia.

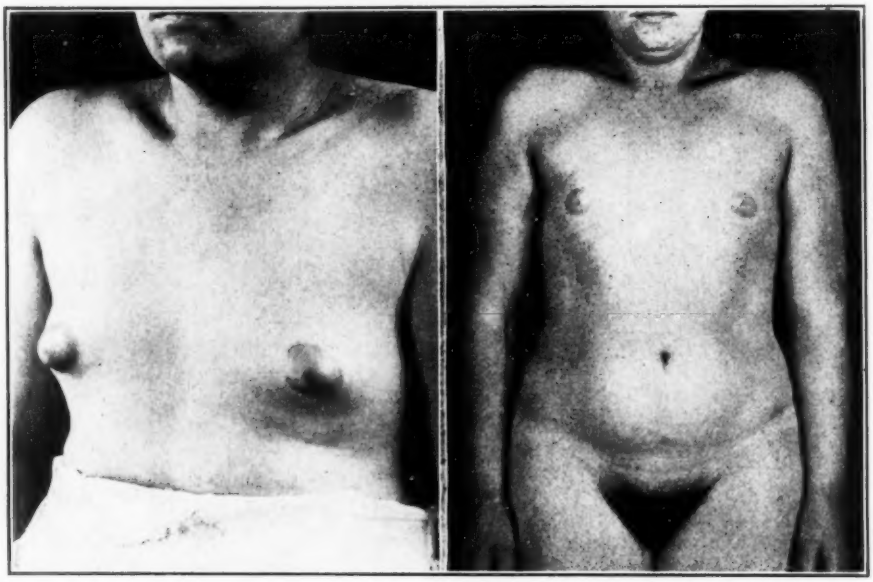


Fig. 13.—Growth of breasts from 100,000 R.U. progynon – B. R. P., aged nineteen years. Primary amenorrhea Group I, marked hypodevelopment of all secondary sex characteristics. Has had 5 successive periods under treatment. Distinct change in psychic outlook.

Hormone determinations of the urine showed neither estrin nor prolan but the development of breasts, external genitalia, and female body contour was indicative of some ovarian function.

Under treatment with progynon B, one patient has had 4 successive periods, and three one period each. The quantity of flow was in general greater than in Group I. The possibility of continued menstruation without further treatment exists in these patients (unlike Group I), because their ovaries are functioning. It will probably be necessary to continue the administration of progynon B until the uterus has attained adequate development.

Endometrium removed prior to the onset of bleeding from one patient showed secretory changes. Since no corpus luteum hormone was administered, the progestrin was derived from the patient's ovaries.

B. *Secondary Amenorrhea.*—In order to rule out spontaneous return of menstruation, we have excluded all cases of secondary amenorrhea of less than one year's duration. The number of cases fulfilling this requirement is eleven. The duration of the amenorrhea ranged from one to eight years. In addition, we have included a thirty-two-year-old patient who has menstruated regularly once in three months since the onset of her periods at the age of thirteen years. Also another patient who during the past six years has not menstruated on two successive months, the periods of amenorrhea ranging from three to twenty-two months. Table II shows the significant physical and laboratory findings together with the results of treatment.

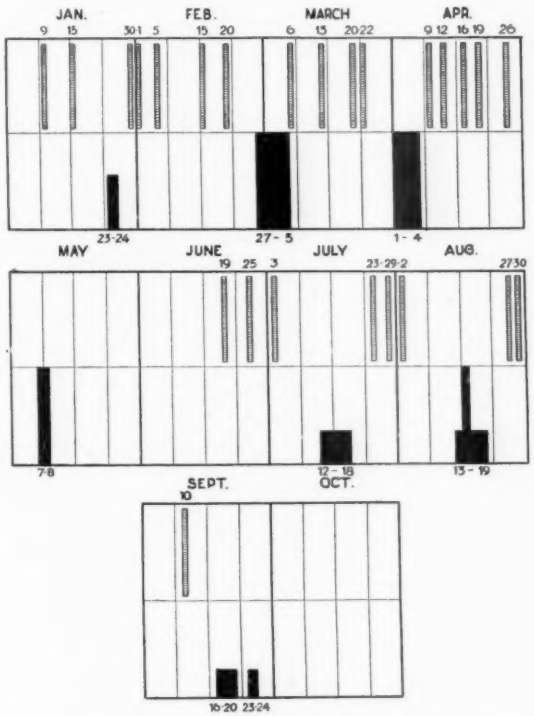


Fig. 14.—B. S., aged nineteen years. Secondary amenorrhea, three years' duration; basal metabolic rate minus 18 per cent. Some hypoplasia of breasts and uterus. All previous medication had failed. Only 20,000 R.U. of hormone required to bring on the first period.

Our criterion of a successful result is the occurrence of at least 3 successive periods. Case 5 must be excluded because the duration of treatment has been insufficient (two months). Of the remaining 11 cases, 8 satisfy our criterion. Bleeding, in most instances, has been more profuse than in the group with primary amenorrhea. The quantity of estrogenic hormone required to initiate the first period is considerably less (about 50,000 R.U.). In 2 patients, however, bleeding did not begin until approximately 100,000 R.U. had been administered; subsequent periods resulted from much smaller doses.

It is too early to determine the ultimate result of this therapy. Treatment is being continued in two cases. In 3 patients, each of which had 3 or 4 successive periods, there was no further bleeding during the succeeding months when treat-

TABLE II. SECONDARY AMENORRHEA

NUMBER	AGE	DURATION OF AMENORRHEA	OBESITY	HIRSUTISM	GENITAL HYPOPLASIA	ESTRIN R.U. LITER	A.P.H.	B.M.R.	NUMBER OF SUCCESSIVE PERIODS	MENSTRUATION WHEN TREATMENT STOPPED
401043	21	6 yr.	+	–	Moderate	4	0	Not done	4	No
76814	21	2½ yr.	+	–	External and internal	0	0	–14	3	Failed to return
365777	33	8 yr.	+	–	Ext. and internal (marked)	(Not done)		–10	3	Failed to return
256512	25	1½ yr.	+	–	Ext. and internal	0	0	+11 – 1	4	Failed to return
338313	32	5 yr.	+ (Basophilic adenoma?)	+	Internal	0	0	–18	2 (Insufficient treatment)	No
409885	23	1 yr.	–	–	Ext. and internal	0	0	–10	3	No
386304	19	3 yr.	–	–	Internal	4	0	–18	6	Treatment still in progress
358137	32	1½ yr.	–	–	Internal	9	0	Not done	2	Treatment still in progress
28633E	17	1½ yr.	– – –	–	Ext. and internal	(Not done)		Not done	0 (94,000 R.U.)	3 successive periods with follutein, none since
300879	36	2 yr.	–	–	None	(Not done)		Not done	2	No
385681	35	1 yr.	–	–	External	9	0	–4	5	1 (Thus far) all scanty
96627	32	Every 3 mo.	–	–	External	4	0	–1	4	No
E. G.	29	3-22 mo.	+	+	Internal (mild)	8	0	–3	6	2

ment was stopped. Three other patients have not returned to the clinic. One patient has had a single period and another two successive periods since the cessation of treatment.

The possibility for spontaneous continuation of menstruation exists here because of the presence of functioning ovaries. In some cases it may be necessary, however, to stimulate subnormal ovarian function by the use of anterior pituitary hormones. In other cases, further treatment with estrin may be required before the genital tract attains sufficient development to respond to the patients' own estrin supply. It is encouraging, nevertheless, to know that patients with long-standing secondary amenorrhea, many of whom were previously unsuccessfully treated by other means, had cyclical periods when adequate amounts of estrin were administered.

At the present time we do not know the quantitative requirements of follicle-stimulating and luteinizing hormones for menstruation. Whether they will be of the same order of magnitude as estrin is unknown. Work has been hindered because we have been unable to secure the gonadotropic hormones in high concentration, and furthermore because urinary prolan* (antuitrin-S or follutein) contains both prolan A and B. Castrate human urine is the only source for the follicle-stimulating hormone alone. A knowledge of the chemistry of these hormones would probably be as productive here as it has been for estrin.

CONCLUSIONS

1. A group of primary (12 cases) and secondary (13 cases) amenorrhea has been treated with large doses of estrogenic hormone (progynon B and amniotin).

2. We have confirmed Kaufmann's observation that 40,000 R.U. of estrin are required to produce cyclical bleeding and to build up the proliferative phase of the endometrium.

3. Cyclical bleeding cannot be differentiated by the patient from normal menstruation.

4. Dosages of 100,000 R.U. or more, are usually required to bring on the first period in cases of primary amenorrhea, and about 50,000 R.U. in secondary amenorrhea.

5. Dosages of 50,000 R.U. are necessary to initiate the growth of the breasts, mainly the duct system.

6. Dosages of more than 100,000 R.U. are essential to produce growth of a hypoplastic myometrium.

7. In some cases of primary amenorrhea, the breasts, the cyclical bleeding and the myometrium regressed, in the order named, when treatment was stopped.

8. The uterine *anlage* which has failed to develop in the fetus may be brought to some stage of development in adult life by large doses of estrogenic hormone.

9. Spontaneous menstruation may follow the cyclical bleeding induced by estrogenic hormone (as in secondary amenorrhea).

*Urinary prolan is not identical with the real gonadotropic hormone of the anterior lobe!

10. The endometrium which has been built up to the proliferative phase by an external supply of estrin may be converted to the pregravid phase by the patient's own corpus luteum.

We are indebted to Professor Benjamin P. Watson for constant encouragement and advice, and for his placing the large material of the Sloane Hospital for Women and the Vanderbilt Clinic at our disposal. We also wish to thank Drs. John C. Kilroe, Thomas J. Parks, Charlotte H. Phillips and Hans Wiesbader for their kind cooperation and help.

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Primary carcinoma of the fallopian tube is a comparatively rare affection. Etiologically important are chronic salpingitis, benign papilloma, accessory tube and detached fetal cell groups. Frequently, benign tumors are found at the same time in the ovaries and the uterus. In one-third of the cases the disease is bilateral, being most frequently localized in the abdominal part of the tube. Women of from forty to fifty-five years of age are most frequently attacked. The symptoms are very vague, the most important being abdominal pain, menstrual anomalies and bleeding. The diagnosis is difficult and is seldom established before operation. The prognosis is bad. The treatment consists of removal of the uterus and both adnexa, as a rule, by means of supravaginal amputation.

J. P. Greenhill.

THE RÔLE OF ESTRIN AND PROGESTIN IN EXPERIMENTAL MENSTRUATION*

With Especial Reference to the Complete Ovulatory Cycle in Monkeys and Human Beings

Earl T. Engle, Ph.D., Philip E. Smith, Ph.D., and M. C. Shelesnyak, Ph.D., New York, N. Y.

(From the Department of Anatomy, College of Physicians and Surgeons, Columbia University)

THE problem of the causation of menstruation in the monkey or the human being is not yet solved. Three theories are current: (1) It is due to a cessation of activity of the corpus luteum. According to this theory, which is generally accepted clinically, menstruation is thought to be due to the withdrawal of progestin. This theory is necessarily applicable only to the complete ovulatory cycle. Among its adherents Schroeder is eminent. (2) It is due to a lowering of the estrin level. This theory has evolved from experimental work in the monkey in which nonovulatory cycles are the rule during the summer months and not uncommon in the other months. It has been sponsored by Allen (1932, 1933) and by Corner (1933), so that it seems justifiable to speak of it as the Allen-Corner hypothesis. (3) It is due to a direct stimulation of the endometrium by some substance liberated by the hypophysis. In contrast to the two other theories this one involves a positive stimulus and not the withdrawal of a hormone. This theory was advanced by Hartman, Firor and Geiling (1930).

Inasmuch as the present paper will deal largely with the estrin and the progestin withdrawal theories, we will review at this place the data which have led to the postulation of the theory that estrin withdrawal is the factor immediately responsible for menstruation. A brief review of the direct stimulation theory will be included, since an analysis of the data of Hartman et al. shows that menstruation in at least most of their cases can be explained as due to a lowering of the estrin level.

The Estrin Privea (Allen-Corner) Hypothesis.—This theory is based largely on the early experimental work of Allen which has been confirmed and extended by others. The main points of the experimental findings supporting this theory are as follows: If both (or even one) of the ovaries are removed in an adult macaque monkey toward the end of the second week after the last menstruation, the tenth

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to the sixteenth day of the cycle, external bleeding from the interval type of endometrium results in three to five days (Allen, 1927). Even earlier ablation will cause bleeding (Van Wagenen and Aberle, 1931). Aspiration of several large follicles in an adult monkey causes bleeding in six days (Allen, 1926). If a monkey is spayed and estrin injections begun at once bleeding will not occur, or if treatment is delayed for two or three days bleeding may occur but is shorter than it would have been had no treatment been given, even if treatment is delayed to the first day of bleeding. When the endometrium of spayed monkeys has been built up by estrin injections to the interval type, stopping the treatment results in bleeding in five to seven days, and if the level of the dosage is lowered three or four days before the last treatment, bleeding occurs earlier than when a full dosage had been maintained throughout (Allen, 1926). If the lower level of estrin dosage is continued, bleeding also occurs (experiments of Hisaw et al., quoted by Corner, 1933*).

All the above observations on ovarian extirpation followed by bleeding were made on adult or subadult animals. In immature animals in which estrin secretion, as shown by the sex skin, has not yet reached the pubertal level, ovariectomy does not induce bleeding, as shown by Allen in 1928 with 2,500 gm. animals. In frankly immature animals or those nearing maturity in our series (3 of 2,000 gm. body weight, 1 of 3,000 gm., and 1 of 3,200 gm.) unilateral ovariectomy did not result in bleeding by the sixth or by the eighteenth day in 2 animals of 2,500 gm.

It may be clearly accepted that estrin withdrawal in animals whose endometrium had been stimulated by this hormone results in bleeding. It must be recognized, however, that none of these experiments threw light on the question of whether estrin withdrawal will produce menstruation or not if the endometrium has undergone a progestational proliferation, and entered the progravid stage attained just prior to the onset of menstruation in the characteristic complete human cycle.

The Anterior Pituitary and Menstruation—the Direct Stimulation Theory of Hartman et al.—The pronouncement of Hartman, Firor and Geiling (1930) that menstrual bleeding was a direct effect of a principle of the anterior pituitary, and, therefore, not referable to a withdrawal of a hormone, stimulated investigation. In this work Hartman et al. used extracts both of the anterior pituitary (A.P.) and of pregnancy urine and were under the impression, current at that time, that the gonadotropic principle in pregnancy urine was elaborated by the anterior pituitary and therefore that its injection constituted true pituitary treatment.

1. *The Effect of Anterior Pituitary Extracts.*—An analysis of the data of Hartman and his associates (Protocols 31, 82, 85, 86, and 91) reveals the fact that in all cases in which true anterior pituitary extracts were used, bleeding occurred after the cessation of treatment and therefore lend no support to the idea that a direct stimulus of the endometrium by the pituitary injections induced menstruation. Since the treatments were performed on nonovariectomized monkeys, they are referable to the cessation in the stimulation of the ovary and estrin production concomitant with cessation of the anterior pituitary injections. Saiki (1932), who injected special sheep anterior pituitary extracts and found that bleeding followed the cessation of treatment, interpreted his experiments in this way. He noted a reddening of the sex skin during the injections and when treatment was stopped, the sex skin became pale, a response which is an excellent index of estrin production. When ovariectomized animals were used, the anterior pituitary injection caused no reddening of the sex skin, and cessation of treatment was not followed by bleeding. Thus the data of Hartman and of Saiki are uniform. The latter, however, contrary to Hartman, referred his findings to a stimulation of the ovary by the anterior pitu-

*Van Wagenen and Aberle have observed that bleeding occurred following section of the spinal cord, a phenomenon which they refer to as a vascular disturbance in the ovaries due to the cord section. Menses are subsequently resumed.

itary and an accompanying change in estrin production. His interpretation is in accord with all other work on the reproductive system.

One class of experiments might be interpreted as supporting the theory that the pituitary elaborates a "bleeding factor" if it were not for the fact that recent extensive work has thrown light on the response of the ovary to long-continued anterior pituitary injections. Hisaw and his associates noted that bleeding may occur during prolonged anterior pituitary injections. Our data, confirming observations of Hisaw, show that in these long treatments there is at first an intense reddening of the sex skin which may be followed by a blanching and bleeding in spite of the continued injections. It is well known that anterior pituitary implants or injections cause various degrees of follicular development in the monkey ovary from large follicles to cystic degeneration (Allen, Hartman and Squier, Hisaw et al., Engle). It is evident that the ovary in these long treatments does not continue to produce estrin at a high level, and that the bleeding in these cases is caused by a drop in this level due possibly to the exhaustion of the ovaries.

The data at present available on injection of anterior pituitary gonadotropic hormone are not readily interpreted in support of the contention that menstruation is due to a direct stimulation of the uterus by this hormone. In the experiments quoted menstruation can be referred as in the estrin-injection experiments to a drop in the estrin level.

2. *Pregnancy Urine Extract.*—The injection of adequate doses of pregnancy urine extract in pubertal, adolescent, or mature monkeys invariably produces bleeding. The evidence from both the sex skin and ovarian changes shows, however, that this bleeding can be explained by a lowering of the estrin level and not to the direct action of the pregnancy urine extract on the endometrium. They, therefore, supply one more type of case in which bleeding from an interval type of endometrium is referable to estrin privea.

Hartman, Firor and Geiling (1930) have presented several cases (Cases 125, 20, 69, and 82) in which pregnancy urine injection caused bleeding. These were included in their data which they presented to show that anterior pituitary extract directly stimulated the bleeding of the endometrium. Their Monkey 125 showed red blood cells in very small numbers on days four and eight of the pregnancy urine injections. Monkey 20, an adult, showed very slight bleeding on the sixth day. Monkey 69, multipara, began bleeding on the fifth day of the injections and continued five days after the injections ceased. In our experience we have evidence from an extensive series confirming this type of bleeding.

A sample of these data is presented by two cases, Monkeys 166 and 170. Both animals weighed 4,450 grams. Both had a single ovary removed. Anterior pituitary extract was given to one, and pregnancy urine to the other. Case 166, receiving anterior pituitary extract, did not bleed in a ten-day period. Monkey 170 bled on the third day of the treatment, fourth day after removal of one ovary. With anterior pituitary treatment estrin production is increased, as judged by the activation of the sex skin (Hisaw et al.; Engle). With pregnancy urine, however, reddening of the sex skin does not occur, or if present in the adult cycle, is caused to fade rapidly.*

*In addition to this most important factor is the well-recognized tendency of the earlier and cruder extracts, at least, to produce local genital congestion in both monkeys and human beings. This may be so pronounced in some instances of monkeys which have been treated for a long time that a strong case could be made for the view that the bleeding was due to congestion and diapedesis of red blood cells, and not solely to estrin withdrawal.

The uterus of the monkey is probably highly sensitive to many substances and does bleed easily. Hartman has recently reported bleeding after injection with liver extract. Hartman's criteria of bleeding are quantitatively very different from those considered here, for he has considered a few R.B.C. in a microscopic field to be "bleeding" or still more extreme "menstruation." We have been concerned with uterine bleeding readily seen with the unaided eye.

It must be stated, however, that our observations reported above, and those to be presented later in this paper differ in one respect from some of those of Hartman, in which the animals were reported to have been hypophysectomized. We are thoroughly aware that complete hypophysectomy may modify the response to pregnancy urine injections or to any other hormone affecting the genital system.

It seems clear that at least one of the causative factors in the production of uterine bleeding with pregnancy urine injections in normal animals is a lowering of the estrin level induced by the repressing action of the injections on the ovaries. As in the case of estrin injections or ovariectomies, however, none of these cases reveals the causative factor of menstruation, when a progestational proliferation has taken place as in the complete ovulatory cycle. In order to determine the factor responsible for menstruation under such a condition, experiments with a progravid endometrium are necessary. Such experiments will be described in the two following sections.

EXPERIMENTAL DATA

Inhibition of Expected Uterine Bleeding by Progestin.—Data from this and other laboratories summarized in the preceding paragraphs show that estrin withdrawal will cause uterine bleeding in adult or subadult monkeys whose endometrium has not undergone a progestational proliferation. As there stated, these data do not show, however, for the complete ovulatory cycle that estrin withdrawal is the primary or even an important factor in the induction of menstruation for in the ovulatory cycle, presumably the usual type in the human being, a progravid endometrium develops. To aid in determining the important immediate factor, estrin or progestin withdrawal, operating in the complete cycle in the induction of menstruation, experiments were planned to answer the following questions: (1) Will the administration of progestin following high estrin secretion or administration and its subsequent withdrawal prevent menstruation? (2) If so, will continued administration of progestin continue to prevent menstruation? (3) Will the administration of estrin consequent to progestin injections (with the development of a progravid endometrium) prevent menstruation if the injection of progestin is stopped?

The experiments outlined under (1) and (2) above will be discussed in this section.

In the first series of these experiments, adult or subadult monkeys were treated with the follicle-stimulating fraction of the anterior pituitary which, when given subcutaneously, causes no luteinization. There is no advantage in the use of the extract of the anterior lobe over the direct administration of estrin, except that a more uniform and constant liberation of estrin is achieved. No difference has been noted in the structure of the endometrium between these two methods of treatment. With either method a good interval endometrium is developed. The addition of

estrin to the anterior pituitary treatment was perhaps superfluous, but it ensured a maximal development of an interval endometrium, and assured the experimenter that if the treatment was stopped, bleeding would ensue four or six days later.

Hisaw, Meyer and Fevold (1930) have demonstrated that after preparation of such an interval endometrium in the monkey, a progestational change may be brought about by an active principle of the corpus luteum, which they have called "corporin." A similar, probably identical, hormonal principle has been prepared by Corner and W. Allen, which is assayed in rabbit units. The preparations used in these experiments were made according to W. Allen's (1930) recent methods, and following Corner, we have termed this material "Progestin."*

In certain cases (Fig. 1), the preparatory treatment had consisted of follicular stimulation and estrin injections, these being followed by bilateral ovariectomy. Any one of these treatments alone would have resulted in uterine hemorrhage on the fourth to sixth day after the last day of processing. However, after progestin

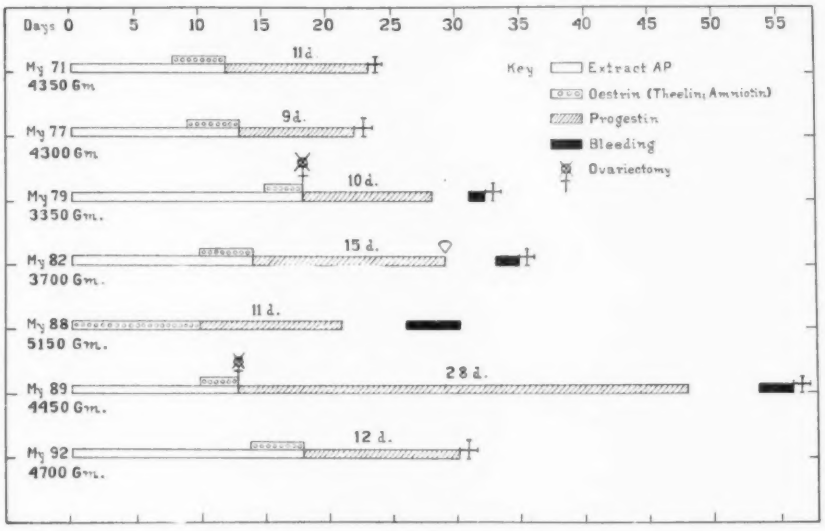

Fig. 1.

therapy, in dosages as low as 1 rabbit unit per day, bleeding has invariably been inhibited. In this series one animal (Case 89) was treated with progestin for twenty-eight days. Bleeding resulted only after the cessation of treatment, with blood in the vaginal lavage on the fifth day after cessation, and a profuse flow, with clots of blood and endometrial shreds on the sixth day.

Detailed protocols of four of the seven animals in this series are given, and the data for the series are graphically summarized in Fig. 1. There have been no failures in preventing bleeding so long as corpus luteum was administered. Several animals, Cases 71, 77, and 92, were sacrificed to obtain histologic material. The remaining four were permitted to progress to the degenerative phase, and bleeding occurred on the fourth, fifth, and sixth days after cessation of treatment. In ad-

*In our experiments, progestin has been recorded in daily dosages of grams equivalent of fresh gland. 1 c.c. of our preparation is roughly equivalent to one rabbit unit. The daily dosages given have been approximately 1, 1½ and 2 rabbit units. We do not know the minimal dose, or the minimal time required to produce a typical progestational endometrium. Such a modification of an interval endometrium may be caused by 1 c.c. daily (35-38 grams equivalent) or 1 rabbit unit daily for 10 days (Smith and Engle, 1932).

dition to the animals reported here, we have in other animals demonstrated the adequacy of the progestational proliferation by the mechanical stimulation of a decidual response, comparable to that reported in early pregnancy by Streeter and Hartman.

PROTOCOLS

Monkey 71 ♀.—4,350 gm., uterus 10 mm. broad on digital palpation. A.P. (aqueous fraction of pyridine extract of dried sheep anterior pituitary) 40 c.c. (13.3 gm. dry powder) twice daily 10 days, subcutaneously. Last 4 days of A.P. treatment 19 c.c. Theelin given concurrently (50 R.U. per c.c.). Progestin instituted day after last A.P.-theelin treatment and continued for 11 days. Daily dose 45 gm. equivalent, fresh hog corpora lutea. No bleeding for the entire period. Autopsy on twelfth day after cessation of theelin.

Monkey 79 ♀.—3,350 gm. A.P. 30 c.c. (10 gm.) for 10 days S.C. + 8 days (21 c.c. 7 gm.) intravenously. Theelin on last 3 days (total 9 c.c. 450 units). Both ovaries removed. Uterus 11.4 by 9 mm. First injection of progestin on day of operation. Progestin for 10 days (1 c.c. = 38 gm., total 541 gm. fresh hog corpora lutea). Tolerated progestin badly, blood in vaginal lavage, on fourth day after cessation of progestin treatment. Autopsy.

Monkey 82 ♀.—3,700 gm. A.P. 14 days (10 gm.), last four days 16 c.c. (800 units) theelin. Progestin on day following last injection. Theelin continued for 15 days. Total 1,260 gm. fresh hog corpora lutea. No blood even on vaginal lavage. On last, fifteenth day, of progestin treatment uterus measured 16.1 by 12.3 mm. Sample of uterus removed, next day slight blood in vaginal lavage. Good external flow on fifth day after last progestin treatment. Autopsy on second day of bleeding, uterus 37.8 cervix-fundus 15.2 infratubal width, 14 greatest depth.

Monkey 89 ♀.—4,450 gm. A.P. 13 days; last three days of this course 14 c.c. (700 units) theelin. Day following last injections both ovaries removed. Uterus 18.0 by 14.7 mm. Progestin given on day of operation and for 28 days. Total 1,781 gm. fresh hog corpora lutea (63.6 gm. daily); no vaginal blood during the course of treatment. Slight vaginal bleeding on fifth day after last injection. Profuse flow with large clots on sixth day. Autopsy second day of bleeding. Uterus 35.4 by 19.8 by 13.7 mm.

It is, thus, conclusively demonstrated that the administration of progestin will prevent bleeding after a complete withdrawal of estrin. Furthermore, after a progravid type of endometrium has been produced by the progestin injections, a condition identical with the complete ovulatory cycle, the continued injection of progestin will continue to prevent menstruation, a flow not occurring until four or six days after the progestin injections are finally stopped.

The Failure of Estrin to Prevent Bleeding From a Progestational Endometrium.—The data presented above demonstrate that experimentally the usual bleeding of estrin privea may be prevented for as long as a twenty-eight-day period of progestin administration. This conforms to the usual clinical concept of menstruation that cyclic bleeding most commonly occurs after the breakdown of a corpus of ovulation in the nongravid cycle.

It now remained to determine whether or not the injection of estrin would prevent menstruation if commenced at the time that a series

of progestin injections, which had induced a progravid condition of the endometrium, were discontinued.

The animals were pretreated as before with an hypophyseal extract, with estrin and then for eleven days with progestin. During this period there were no red blood cells in the vaginal lavage. On the day following the last progestin treatment, estrin, 100 to 200 units daily, was given, and continued for various periods. This amount is much more than sufficient to prevent bleeding from an interval endometrium after bilateral or unilateral ovariectomy.

After the progravid endometrium had been developed, however, estrin, though given immediately and consecutively, and without lowering the dosage, did not prevent bleeding. Endometrial erosion occurred within the expected time. Estrin did not prevent the loss of tissue, the breakdown of the peripheral capillary bed, or change the duration of the bleeding.

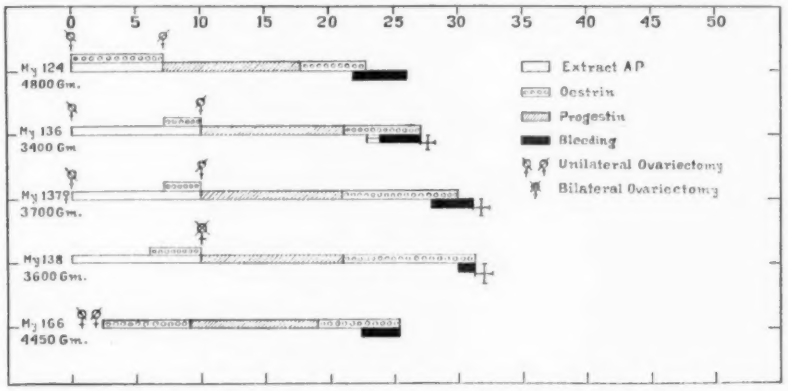

Fig. 2.

The experimental conditions were similar to the human menstrual cycle in which uterine hemorrhage from a progestational endometrium invariably occurs in the presence of an abundance of estrin in the circulation.

The data are graphically presented in Fig. 2 and in the detailed protocols.

PROTOCOLS—SECOND SERIES

Monkey 124 ♀.—4,800 gm., menstruating Dec. 8 to Dec. 11, 1932. December 27, left ovary with corpus luteum removed. A.P. and theelin, 7 days. Right ovary removed on eighth day. Progestin, 50 gm. equivalent daily 550 gm. total for 11 days. Estrin (theelin) 2 c.c. daily five days. No R.B.C. on lavage on days 1, 2, 3, or 4 after cessation of progestin. On the fifth day, good external bleeding. No further estrin treatment. Bleeding on days 6, 7, and 8.

Monkey 136 ♀.—Young animal, 3,400 gm. Right ovary removed, 5 by 4.2 by 3.1 mg. Pyridine extract A.P. 21 c.c. = 7 gm. dried sheep A.P. for 10 days, last 3

days concurrent injections 9 c.c. estrin (theelin) 450 R.U. Left ovary removed, 6.8 by 4.7 by 4.0, 92 mg. uterus 13.8 by 8.7. Progestin on day of operation and for 11 days (385 gm. total dose). No blood on lavage during treatment. Estrin (theelin) 2 c.c., 200 R.U., given on day following last progestin treatment. Continued 6 days (1,200 units total). Blood in vaginal lavage on third day estrin treatment. External blood on fourth day; on fifth day profuse bleeding with clots; on sixth day no external blood, few R.B.C. on lavage; on seventh day no R.B.C. Autopsy. Uterus 35.2 by 15.8 by 11.4. Bleeding during estrin treatment on fourth, fifth, sixth, and seventh days after last progestin treatment.

Monkey 138 ♀.—3,600 gm. Ten days A.P. 21 c.c. (7 gm. dried sheep gland) aqueous pyridine method. Concurrent estrin injection last 4 days (9 c.c., 450 R.U.). Ovariectomy eleventh day. Right ovary 139.3 mg. Left ovary 138.6 mg. Uterus 10.9 by 10.4. Progestin (1 c.c. = 35 gm.) 70 gm. daily for 11 days. Estrin started day following last progestin treatment. Vaginal lavages daily throughout. Animal tolerated progestin badly. Estrin 200 units daily for 11 days, on eleventh day bleeding. Autopsy on eleventh day. Uterus 33.0 by 14.8 by 12.0. Great loss of weight and effect of toxicity of extract. No pathologic lesions seen at autopsy.

Monkey 137 ♀.—3,700 gm. Right ovary removed, 6.6 by 4.1 by 4.8, 85 mg. Left ovary 7.0 by 3.5. A.P. subcutaneous 10 days (7 gm. dried sheep A.P. aqueous pyridine method). Last 3 days concurrent injection estrin (theelin) twice daily (total 500 units). Left ovary removed, 7.6 by 6.2 by 4.8., 133.3 mg. Progestin on day of operation and for 11 days 50 gm. daily, total 550 gm. fresh corpora lutea. Estrin (theelin) on day following last treatment 2 c.c. daily. Vaginal lavages daily. No. R.B.C. on days 1, 2, 3, 4, 5, or 6. On day 7 good external flow, continuing through days 8, 9. Autopsy on ninth day after cessation of progestin. Uterus 35 by 14.8 by 9.0.

Monkey 166 ♀.—4,450 gm. Menstrual period October 2 to 5. Ovaries removed, right October 12 and left October 24. Uterus 11.7 by 9.1 mm., uterine bleeding following ovariectomy. Estrin 200 units daily (amniotin in oil) during bleeding (2 days) and for 5 days thereafter. Extract progestin (6 months old, 57 gm. fresh tissue daily, slightly more than 1 rabbit unit) for ten days. No R.B.C. in lavage in this period. Color faded by days 8 and 9. On day after last progestin treatment, estrin (amniotin in corn oil) 300 units daily. No R.B.C. in lavage on estrin days 1, 2, 3. On day 4, the fifth day after last progestin injection, external bleeding. Bleeding 3 days during continued estrin injections.

Progestin has prevented the usual and expected bleeding of estrin privea and led to the formation of a typical progestational endometrium. When this endometrial condition has been established, as it is in the ovulatory cycle of the monkey or human being, subsequent menstruation, with its morphologic equivalents, occurred in the presence of large amounts of estrin.

DISCUSSION

The Allen-Corner hypothesis that menstruation is due to estrin privea has been based largely on the experimental results on the monkey. The available data regarding the hormonal relations during the human cycle offer certain obstacles. The data in this respect are not so abundant as might be hoped but are quite uniform.

Allen, Pratt and Doisy (1925) have shown that the human corpus contains considerable estrin (40 M. U.) shortly after ovulation, which decreases as the luteal body ages. The smaller follicles approaching the next ovulation term also produce estrin.

Estimates of the blood estrin vary, but it is found in considerable quantities immediately before menstruation. In their most recent contributions Frank and Goldberger (1930, Chart 1, 1931, Fig. 4) have presented graphs bearing composite data for women in normal menstrual cycles, and they say (1931, reprint page 7) "in the fully normal, fertile woman, one mouse unit (of estrin) can be demonstrated in 40 c.c. of blood from seven days before the menses *to* the onset of menstruation." Earlier (1928, reprint page 5) they say "in from three to one day before the anticipated flow 100 per cent showed at least a mouse unit" in from 20 to 40 c.c. of blood, i.e., 25 units per l. and further, page 7, "the menstrual blood shed on the first day usually contains a considerable quantity of female sex hormone." These workers (1930) also found urinary estrin in quantities in the five days immediately preceding menstruation. Frank and Goldberger's data do not support the Allen-Corner theory that menstruation is due to estrin privea.

Frank's opinion may be stated clearly that the blood estrin drop occurs mainly after bleeding has started, although occasionally the day before the bleeding.

An important series of papers on the estrin level during the normal menstrual cycle are those of Siebke. Reinvestigating Frank and Goldberger's findings, Siebke (1929) reported on blood estrin in normally menstruating women. His data are summarized in his Fig. 2, showing a preponderance of positive tests occurring during the week preceding menstruation. "Die stärkest Konzentration fanden wir etwa am 3. Tag ante menstruationem."

Siebke (1930) has also analyzed the urinary estrin of a series of women and has presented clear case histories and graphs of the estrin excretion of individual cases, recorded for three-day periods of the menstrual cycle. Many of Siebke's patients do not fall into the group of the mythically "normal," and it is impossible to treat the group as a whole. Selected instances, however, indicate that the urinary estrin is high during the period of follicular maturation, falling rapidly after the time of probable ovulation (Curve I, p. 1606), days twelve to ten before the next menstruation. In other cases (Curves V, VIII) the high estrin excretion is on days seven to five and twenty to fourteen before the next period. In a later report Siebke (1931, p. 425) gives the average values for urinary estrin, showing a peak on the twelfth to tenth days antemenstruum.

It must be assumed that the renal threshold is one factor in the difference between the blood and urinary values of estrin. These quite irregular values differ from those of Frank and Goldberger, but are equally difficult to fit into a theory of estrin privea menstruation because the period of low estrin in Siebke's cases is too distant in point of time from the next menstruation.

Both Kaufmann (1932) and Clauberg (1933) have reported the production of progestational endometriums in ovariectomized women by the use of follicular hormone followed with corpus luteum hormone.

Loeser (1933), however, has observed the bleeding response in several cases. The patient in the first case, twenty-eight years of age, was one with primary amenorrhea. She was first treated with follicular hormone, 400,000 M.U. over a period of thirty-eight days, and this was followed by corpus luteum hormone, 40 Rab. U. for four days. Typical bleeding began two days after the last treatment and continued for five days.

The period of this treatment had been forty-four days. In the next experiment with the same patient it was reduced by one-half. Estrin, 330,000 M.U. for sixteen days and progestin, 50 rabbit units, for five days. Bleeding as before occurred one day after the last treatment, and lasted for six days. This was repeated with the same dosage and time factors and the bleeding was the same. The curetted specimens were studied by Robert Meyer and reported to be of the premenstrual stage which had not reached the end of the secretion phase.

In a second case, a thirty-eight-year-old primary amenorrheic, 300,000 M.U. of estrin and 50 rabbit units of progestin in twenty days resulted in bleeding on the second day after cessation of treatment of the progestin injections. Two other cases of secondary amenorrhea were similarly treated. The production of a progravid endometrium with good glycogen production is attested by Robert Meyer.

The present evidence of the human cycle thus leads us to believe that menstruation, usually in the human being from the degeneration of a progravid endometrium, occurs in the presence of an abundance of blood estrin. The experimental data also show that menstruation also occurs in the presence of a high estrin level and fortifies the opinion that when the corpus luteum ceases its secretion, the estrin present cannot further develop the endometrium or maintain its progravid phase. It then begins involution and menstruation takes place.

SUMMARY

1. It is generally accepted that in the mature monkey, uterine bleeding occurs after deprivation of the estrin supply of the animal by any method.

2. This bleeding can be prevented by the administration of a hormone of the corpus luteum, progestin. This prevention has been for the duration of the treatment, in one case as long as twenty-eight days, though usually for eleven or twelve days. Bleeding occurred three to five days after the cessation of progestin treatment, and only then.

3. Uterine bleeding which follows cessation of progestin therapy occurs within the expected time, even though estrin administration is instituted at once and continued until bleeding occurs.

4. Evidence from other investigators dealing with the human cycle is cited, indicating that in the human being also, in the ovulatory men-

strual cycle menstruation results from a cessation in the secretion of the corpus luteum, and that it occurs in the presence of a high estrin content of the blood.

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BLOOD LIPIDS IN THE PUERPERIUM

ELDON M. BOYD, M.A., M.D., C.M., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology, The University of Rochester, School of Medicine and Dentistry)

DURING the past three years, investigations have been performed in the laboratories of this department with a view to establishing the significance of changes in fat metabolism during pregnancy and of their possible relation to disease in gravid women. The work began with a study of micromethods for the estimation of all blood lipids.[1] These methods were then applied to the analysis of blood in pregnant women, and it was found that there was a marked elevation of the values for plasma lipids at the end of pregnancy.[2] Certain lipids, particularly neutral fat, were increased more than others. The lipid content of the red blood cells was shown to be unchanged and hence only minor differences were recorded in whole blood.

A reason was then sought to explain why the blood plasma of pregnant women contained more fatty substances than normally. It was recognized that the fat content of the fetus begins to increase about the same time that the maternal blood lipids rise in value. Hence it was suggested that the increased concentration of maternal plasma lipids may act as an increased pressure head, forcing lipids into the umbilical circulation, as it were. In support of this view, the human placenta was found to add lipids to umbilical blood, from whence they were absorbed in large amounts by the fetus.[3] A well-nourished

human fetus at birth was estimated to absorb from umbilical blood between 40 and 50 gm. of lipids per day, of which 75 per cent was phospholipids. These results suggested that the lipemia of pregnancy may be related to the uptake of lipids by the fetus in utero. It is recognized that this relation need not hold for every species of animals; in several species, for example cows, rats, and rabbits, there is actually a decrease in the blood lipids during pregnancy. Fat metabolism varies appreciably from one type of animal to another, especially between herbivora and carnivora, and the results obtained in one species should not be applied without reservation to the interpretation of the changes in another species.

The lipemia of pregnancy has at various times been proposed as a preparation for lactation, it being suggested that the increased concentration of blood lipids assists the production of milk fat by the mammary glands. This theory obviously applies more especially to the period following parturition and raises the question as to what happens to the lipemia of pregnancy once pregnancy is over. Although often suggested, it has never been satisfactorily proved that the blood lipids in the early puerperium are related to lactation. If there is a relation, then one should be able to demonstrate a difference in the blood lipids between women who lactate normally and those in whom the breasts are dried up for various reasons such as a stillborn infant, etc. This method appeared quite feasible and was adopted in the present investigation to prove or disprove the point.

Apparently the only previous investigation of a similar nature was that of Herrmann and Neumann in 1912.[4] These authors used the semiquantitative methods then available to show that whole blood cholesterol and total lipid decreased during normal lactation but remained elevated when lactation did not occur. More recently, Harding and Downs[5] have shown that the "lipoid phosphorus" of blood plasma declines after delivery less rapidly if milk secretion is small. Practically all those who have reported on blood lipids during pregnancy (for list of references see Boyd[2]) have also included readings during the puerperium but did not contrast the changes in normal lactation with those in a "dry puerperium." In the present investigation all lipid groups present in whole blood, plasma and the red blood cells were separately estimated and compared in puerperae of these two types. The changes in the lipid composition of the white blood cells during the puerperium have been reported by Boyd.[6]

METHOD

The investigation was performed on twelve patients from the Obstetrical Divisions of the Strong Memorial Hospital. Seven of these were primiparas and five multiparas. In all of them pregnancy had been normal and delivery was not accompanied by any untoward event such as excessive bleeding, marked perineal tears, etc. In

nine cases lactation set in with the usual amount of milk flow while three patients were delivered of stillborn infants or the infant died shortly after delivery and the breasts were dried up by the use of a binder, limiting fluids, etc., in the usual manner. The puerperium was normal with the absence of elevated temperature, toxic symptoms, etc., in all patients studied. Throughout the course of the experiment, the patients were kept in bed on a balanced hospital diet.

Blood for lipid analysis was taken on four occasions, namely before delivery and before labor was definitely established, on the first or second day postpartum, again on the third or fourth day, and finally just before the patient was discharged on the tenth to twelfth days. A sample of blood consisted of 20 to 25 c.c. removed from the arm veins in the morning following an all-night, fifteen- to sixteen-hour fast.

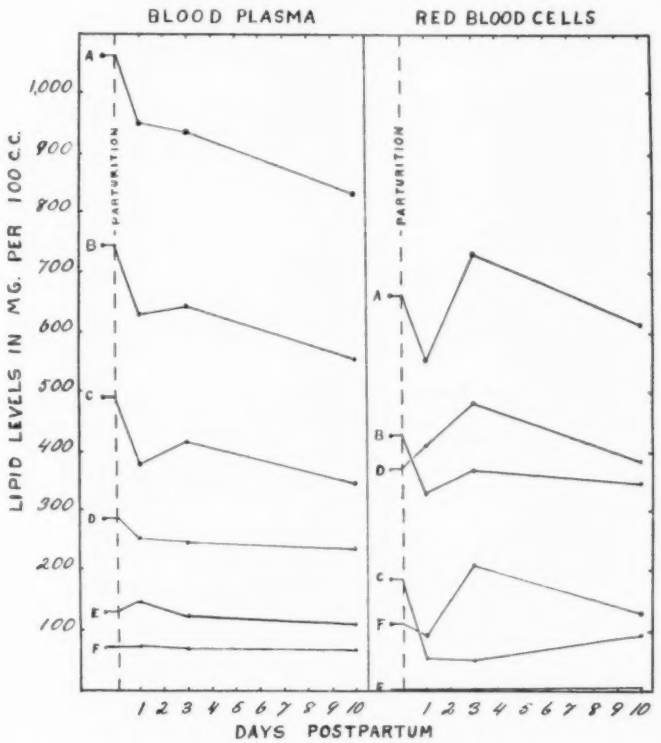

Fig. 1.—The concentration of lipids in blood plasma and the red blood cells during the puerperium in a seventeen-year-old primipara, nursing her baby with an abundant flow of milk on the third day postpartum. Curve A, total lipid; curve B, total fatty acids; Curve C, neutral fat; Curve D, phospholipid; Curve E, ester cholesterol; Curve F, free cholesterol.

The sample of blood was citrated, 5 c.c. removed for whole blood analysis and the remainder centrifuged to separate cells and plasma. Values for all lipids were then determined in whole blood, plasma, and the red blood cells, using the Bloor oxidative microtechnic as modified by Boyd.[1]

RESULTS

Comparatively slight variations were encountered in the lipid content of whole blood following delivery. In the nine patients in whom normal lactation occurred there was a fall in the total lipid values during the first two weeks of the puerperium,

the fall being due principally to a decrease in neutral fat. Phospholipids exhibited very little change while the remaining blood lipids, namely free cholesterol and cholesterol esters, actually rose slightly in value. The changes in whole blood need not be described in any further detail since the results in plasma and the red blood cells were much more descriptive of what was taking place.

The lipid concentration of blood plasma was found to decline consistently after delivery in all cases where normal lactation occurred. On the other hand when the breasts were dried up, plasma lipids fell in value only while the breasts were filling, and then actually rose again as the breasts responded to treatment and began to shrink in volume. A typical example has been selected from each group of cases and presented in Figs. 1 and 2.

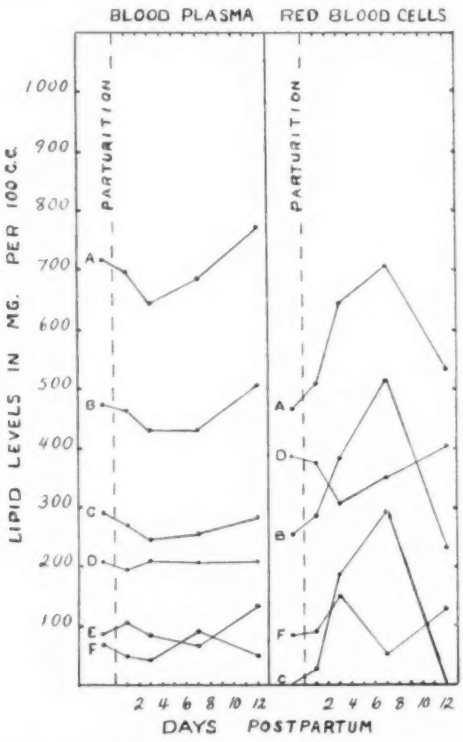

Fig. 2.—The concentration of lipids in blood plasma and the red blood cells during the puerperium in a forty-three-year-old para xi, child stillborn, breasts engorged on the third day postpartum but subsequently dried up. Curve A, total lipid; Curve B, total fatty acids; Curve C, neutral fat; Curve D, phospholipid; Curve E, ester cholesterol and all values equal to zero throughout; Curve F, free cholesterol.

The decline in value of plasma lipids during lactation was in a large part due to loss of plasma neutral fat. On the average, the concentration of plasma neutral fat fell from 353 ± 75 mg. per cent at delivery to 275 ± 115 mg. per cent at the twelfth day postpartum (the figures given are means ± the standard deviation). After neutral fat, the greatest decrease was found in the phospholipids and next in the free cholesterol and ester cholesterol. Changes in the cholesterol fraction were comparatively slight.

When normal lactation was prevented by drying up the breasts, the downward trend in the concentration of puerperal plasma lipids was halted, as illustrated in Fig. 2. In the first three or four days of the puerperium, while the breasts were

filling, the plasma lipids fell in value but once the breasts began to decrease in size the plasma lipids rose again until in some cases they were even higher than before delivery. All four of the plasma lipids, namely neutral fat, phospholipids, free cholesterol, and cholesterol esters, tended each to rise in value when the breasts were dried up. The increase was independent of the initial values before delivery, taking place whether the initial values were low, as in Fig. 2, or high. Lactation or the prevention of lactation may, therefore, be concluded to have a definite effect upon the values of plasma lipids.

On the other hand, changes were encountered in the lipid content of the red blood cells which were apparently independent of lactation. It has been previously shown[2] that the fatty composition of the erythrocytes is not affected by pregnancy. Following delivery, in a few cases, the concentration of lipids in these cells fell for a day or two, but in practically every case the values rose again and rose considerably above normal limits during the remainder of the first week postpartum. By the end of the second week of the puerperium the values had fallen to normal. The cases presented in Figs. 1 and 2 typify the results obtained. It may be noted that the increased fat content of the red blood cells in the first week or ten days of the puerperium was due in most cases to an increase in phospholipids and free cholesterol although occasionally, as in Fig. 2, neutral fat was responsible for a major portion of the increase. This temporary increase in the lipid content of the red blood cells during the early days of the puerperium was not affected by drying up the breasts, similar results being obtained in both groups of puerperae. It may thus be concluded that lactation affects the lipid content of plasma only and that the temporary hyper values in the erythrocytes are independent of the activity of the breasts.

THE COMPOSITION OF PLASMA FATTY ACIDS

Since lactation or nonlactation was noted to affect only the lipids of plasma, it was considered that further information might be obtained by a study of the iodine numbers of the plasma fatty acids. These were determined by a microprocedure previously described.[1] As far as the author has been able to ascertain, no previous report has appeared on the iodine numbers of the blood fatty acids in the puerperium.

The results have hence been reported in detail in Table I. It will be noted that the values obtained and the trends encountered appeared to be independent of the occurrence of normal lactation, similar changes being recorded when the breasts were dried up. The iodine number of the total fatty acids of blood plasma fell from a mean of 88 before labor to 76 in the first week of the puerperium and during the second week began to rise again to normal, a mean value of 81 being found on the tenth to twelfth days postpartum. Although the means exhibited comparatively minor changes, yet in 10 out of 12 cases the iodine number rose during the puerperium usually after a preliminary fall in the first few days following delivery. These results indicate that immediately after parturition blood plasma contains fatty acids of a more saturated type, that is fewer double bonds and hence a lower iodine number. Toward the end of the first week and during the second week of the puerperium, the saturated fatty acids are gradually replaced by more and more unsaturated fatty acids, thus increasing the value of the iodine number which approaches the value for normal women[1, 2] by the end of the second week postpartum.

These changes in the iodine number of the total fatty acids were found to be due in part if not chiefly to changes in the iodine number of the phospholipid fatty acids. As shown in Table I, the mean value of the iodine number of the plasma phospholipid fatty acids before parturition was 119. On the first to third days postpartum, the iodine number of the phospholipid fatty acids fell in 10 out of

TABLE I. THE IODINE NUMBERS OF TOTAL FATTY ACIDS AND PHOSPHOLIPID FATTY ACIDS IN BLOOD PLASMA DURING THE EARLY PUERPERIUM

CASE	MAMMARY GLANDS	IODINE NUMBER			
		BEFORE DELIVERY	1-3 DAYS POSTPARTUM	5-7 DAYS POSTPARTUM	10-12 DAYS POSTPARTUM
		Total Fatty Acids			
1	Lactating	102	94	--	78
2	Lactating	122	81	80	--
3	Lactating	96	85	103	93
4	Lactating	88	68	81	80
5	Lactating	84	50	57	--
6	Lactating	82	63	76	84
7	Lactating	78	124	61	82
8	Lactating	78	81	86	--
9	Lactating	77	63	72	67
10	Dried up	98	81	78	86
11	Dried up	86	61	72	84
12	Dried up	66	61	71	72
Mean		88	76	76	81
		Phospholipid Fatty Acids			
1	Lactating	174	102	--	88
2	Lactating	148	158	156	--
3	Lactating	142	103	112	135
4	Lactating	136	71	94	152
5	Lactating	121	69	92	116
6	Lactating	100	64	115	--
7	Lactating	96	127	130	--
8	Lactating	93	85	137	140
9	Lactating	78	62	65	117
10	Dried up	130	92	102	128
11	Dried up	105	73	96	128
12	Dried up	102	57	65	114
Mean		119	89	106	124

12 cases, reaching a mean value of 89. From then, in all except 2 cases, the iodine number of the phospholipid fatty acids rose steadily in value, reaching a mean of 106 at five to seven days postpartum and 124 or approximately normal[1, 2] at the tenth to twelfth days postpartum. These results indicate that the phospholipids of blood plasma after parturition exchange their fatty acids for fatty acids containing fewer double bonds; by the end of the second week of the puerperium the composition of plasma phospholipid has returned to normal, in terms of its iodine number.

DISCUSSION

The results of this investigation lead to certain further conclusions concerning fat metabolism during pregnancy. It has been shown that when milk is secreted by the breasts after delivery, the concentration of all lipids in blood plasma falls. The greatest decrease was found to occur in plasma neutral fat; next, in order, phospholipids; and finally the least change occurred in the cholesterol (free and ester) fraction. These changes, which resulted in the disappearance of the lipemia of

pregnancy as described by Boyd,[2] are identical in nature to those found by Bloor[7] to characterize the disappearance of lipemias in diabetes, chronic bleeding, etc. The results, in conjunction with those of a former paper,[2] lead to the conclusion that the lipemia of pregnancy, in its onset, height and disappearance, is in no way different from the lipemias of diabetes, chronic hemorrhage, nephrosis, etc.

On the other hand, it has been shown that when milk secretion is prevented by drying up the breasts after delivery, the fasting level of blood lipids rises rather than falls during the puerperium. Three possible reasons may be advanced to explain this. First, it may be postulated that the process of drying up the breasts by limiting fluids, etc., would also "dry up the blood," and automatically increase the concentration of plasma lipids. If this were so then the percentage of red cells should also increase. As a matter of fact, by doing suitable hematocrit readings, it was found that there actually occurred a slight increase in the percentage of red cells in blood during the puerperium. But this increase was noted in both groups of puerperas, i.e., those who lactated normally and those in whom the breasts were dried up, and there was no appreciable quantitative variation between the two groups. It thus appeared that this explanation was inadequate to account for the rise in plasma lipid values when the breasts were dried up.

Second, it may be proposed that the fasting values of plasma lipids were increased by absorption of lipids from the full but nonsecreting mammary glands. It will be recalled that while the breasts were filling in both groups of puerperas the value of plasma lipids fell and rose only after a binder was applied to the breasts. This may logically account for a slight increase in the level of plasma lipids even after a fast, the milk fats being gradually absorbed back again into the maternal blood stream. By the tenth day postpartum the breasts, if dried up after delivery, are usually quiescent, and yet at this time, the plasma lipids were found still high and even rising in value. Furthermore, the full breasts prevented from secreting milk could contain but a few grams of fat at the most, and it is doubtful if this small amount could have any material effect on the level of plasma lipids over any length of time.

It appears, therefore, that the phenomenon of lactation itself along with the various metabolic and endocrine changes which accompany it, is chiefly responsible for the difference in the trends of plasma lipid values between these two groups of puerperas. In other words, the body reacts to normal lactation by showing declining values for blood plasma lipids, and when lactation is stopped earlier than normal, the function of the body is altered in the direction of a lipemia in blood plasma. Whether the blood plasma lipids fall during lactation because they are secreted in milk or because of the presence or absence

of certain hormones or other effects, cannot be stated at present. The results indicate that the effect of drying up the breasts immediately after delivery is not confined to the breasts alone but is reflected by a change in body function generally.

Certain facts indicate that lactation may not be entirely responsible for the fall in plasma lipids after delivery. First, as noted before, the sequence by which lipids disappear from plasma after delivery is analogous to the sequence in the disappearance of other lipemias in which lactation obviously takes no part. Second, it has been shown that the composition of plasma fatty acids, as indicated by their iodine number, undergoes the same changes following parturition irrespective of the onset of normal lactation. And third, the lipid content of the red blood cells increases temporarily in the first week of the puerperium also independently of normal lactation. These changes are probably referable more particularly to the process by which the lipemia of pregnancy disappears rather than to the changes accompanying the onset of lactation. Since both of these factors come into play in the first week of the puerperium, one cannot state that lactation alone is the factor responsible for the decline in plasma lipid values. It is probably correct to conclude that lactation may *assist* in bringing the concentration of blood plasma lipids to normal values. But there is no doubt that the prevention of normal lactation results definitely in a lipemia.

In the lower animals, lactation may have an effect opposite to the above, i.e., it may cause a lipemia. Lactation produces a rise in blood lipids usually in those animals in which pregnancy causes a lipopenia or decrease in the value of blood lipids (for usage of the term "lipopenia," see Boyd[8]). Thus, lactation in the cow is accompanied by a rise in the value of all blood lipids,[9, 10, 11, 12] in rabbits the blood lipids rise in the puerperium independently of the occurrence of lactation,[13] while in dogs the values fall as in women.[13] It is difficult to reconcile these variations between species: there appear to be certain inherent differences in fat metabolism between species of animals, especially between herbivora and carnivora. The important conclusion relative to the present discussion is that experimental results obtained in animals should be applied by analogy to human subjects with the utmost caution.

Several explanations have been offered as to where the excessive amounts of blood lipids go to once pregnancy is over. It has been proposed that in the puerperium blood lipids are discharged through the bile,[14] in urine, sweat and feces,[4] and in milk. Most of these theories and the more recent discussion of them (see review by Boyd[2]) seem to imply that the fat content of blood is a static value. That is to say, these theories appear to take for granted that if a number of grams of lipids are removed from blood by the liver, kidneys, intestinal

tract, etc., in the puerperium, this removal would cause a lowering of the concentration of blood lipids. Blood lipids are continuously in equilibrium with tissue lipids; if lipids are removed from blood, the loss is made up by the addition of lipids from the fat depots. It is unlikely that any removal, except a very excessive one such as occurs in the increased metabolic rate of fevers,[8] could of itself account for a lowering of the value of blood lipids. It is the factors which influence the *equilibrium* between blood and tissue lipids that we must seek to explain the effect of pregnancy and of lactation. The data presented above indicate that in the puerperium this equilibrium is altered in the direction of a lowering of the level of plasma lipids, but if normal lactation is prevented, the change is inhibited or reversed.

SUMMARY

It has been shown that in the puerperium the blood plasma lipids of women decrease in value, the greatest decrease being in neutral fat, next phospholipid, and least cholesterol and its esters. When normal lactation was prevented by drying up the breasts, the decrease in plasma lipid levels was inhibited, stopped, or reversed.

Evidence was obtained that the lipemia of pregnancy tends to disappear in the puerperium independently of the onset of lactation. It was found that in the early puerperium the plasma fatty acids, especially those in combination with phospholipids, become temporarily more saturated, and this occurred whether or not the patients lactated normally. The red blood cells were also found to exhibit temporary increases in their lipid content in the early puerperium and this likewise resulted independently of the onset of normal lactation. And the sequence of lipid changes in the puerperium was shown to be identical in nature to the sequence in the disappearance of any other lipemia.

This information was taken to indicate that the lipemia of pregnancy disappears after delivery independently of the onset of lactation. It was suggested that lactation may probably assist the decline to normal in the value of plasma lipids. When the breasts were dried up, however, bodily function was apparently altered, resulting in the production of a new lipemia.

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THE EFFECT OF THEELIN ON THE HUMAN VAGINAL MUCOSA

ROBERT M. LEWIS, M.D., NEW HAVEN, CONN.

(From the Department of Obstetrics and Gynecology, Yale University School of Medicine)

AS EARLY as 1904 Joseph Halban[1] by brilliant reasoning arrived at the conclusion that certain phenomena observed in the generative system of the newborn human female depended upon a substance elaborated by the placenta and carried by the fetal-maternal circulation to the infant in utero. The truth of his belief has been surprisingly substantiated by recent discoveries in the field of the sex hormones and their functions.

Bayer and others had already shown that the uteri of newborn girls are larger than those of older children. This fact Bayer considered due to an atrophy following birth. Halban, with clearer insight attributed the enlargement of the uterus, breasts, and also probably that of the external genitalia of the newborn to the presence of a material derived from the placenta. Their diminution during the first weeks after birth he laid to their deprivation of this substance. The uterine blood vessels and mucosa of the newborn he notes in certain cases as presenting pictures "exquisitely like" the menstruating uteri of adults. Edgar Allen[2] and others have shown that in the immature female monkey an hypertrophy of the generative tract like that of the newborn can be reproduced by repeated subcutaneous injections of follicular hormone. Although Halban's autopsied specimens of ovaries, tubes, uteri, and external genitalia were carefully studied, the vaginas were in only a few instances noted as "injected."

It is of considerable interest, therefore, to find that the vaginal mucosa of the newborn girl shows on microscopic section what can best be interpreted as a reaction to the maternal hormones that is at least as striking as that of the uterus, breasts, or external genitalia, and also that during the first few weeks of life the histologic appearance of the vagina, which lacks the stimulus of the maternal hormone, changes enormously. This change apparently also occurs in the vaginas of children prematurely born. At least two instances which have come under our notice would suggest that such is the case.

At birth the vaginal mucosa of the premature or mature child shows a basal layer of compact cells with nuclei which take a deep stain in prepared microscopic sections. This cell layer is thrown into folds and varies in depth throughout its length. Superimposed upon it we find a remarkable series of layers of vacuolated cells which often contain nuclei. Mitotic figures are frequent in this layer. This zone consists of vacuolated cells 20 to 30 or more layers in depth. The surface may show fragmentation possibly a result of postmortem change. In

some sections one can see that the superficial surface is covered with two or three layers of very delicate, elongated, flattened and nucleated squamous cells. We have been unable to detect any definite zone of cornification.

Shortly after birth desquamation of the vacuolated cell layers occurs. In sections taken from the vaginas of children between the ages of two months and before pubertal changes occur, we have noted that the general appearance does not vary greatly. Here we find basal layers with deep staining well-developed nuclei. In number the layers are usually six to ten in depth except where the presence of epithelial plugs increases these figures. Again two or three layers of very slender squamous cells cover the superficial surface.

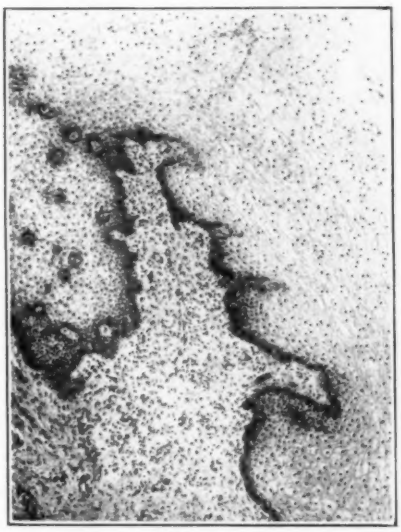

Fig. 1.

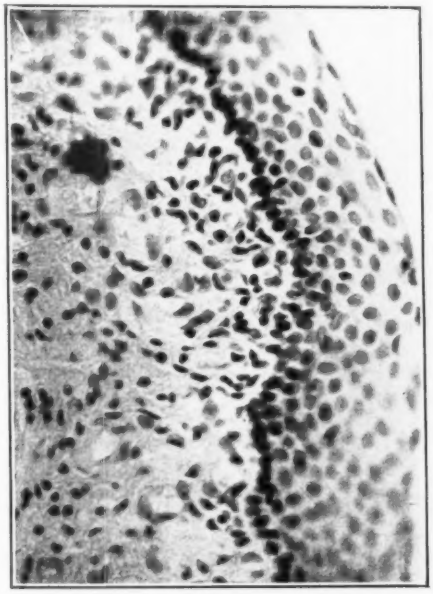

Fig. 2.

Fig. 1.—Section of vaginal mucosa of newborn female child. Note many layers of superficial vacuolated cells in mucosa.

Fig. 2.—Section of normal vaginal mucosa. Child aged two years. Note compact layers of cells in mucosa and absence of vacuolization.

It has been shown,[3] if immature girls are given sufficient follicular hormone hypodermatically over a long enough period, that the vaginal mucosa will again develop an enormously thick layer of vacuolated cells and will resemble the mucosa of the premature or newborn child. In cases, that I have seen, oral administration of the hormone usually produces less striking changes, while the number of units required to effect any change is large. The resemblance of the vacuolated cells in the vaginal mucosa of the immature girl after theelin administration to that of the newborn is so striking that one is forced to the

conclusion that the same agent, namely theelin, must be responsible for the production of the tremendous number of superficial vacuolated cells in both instances.

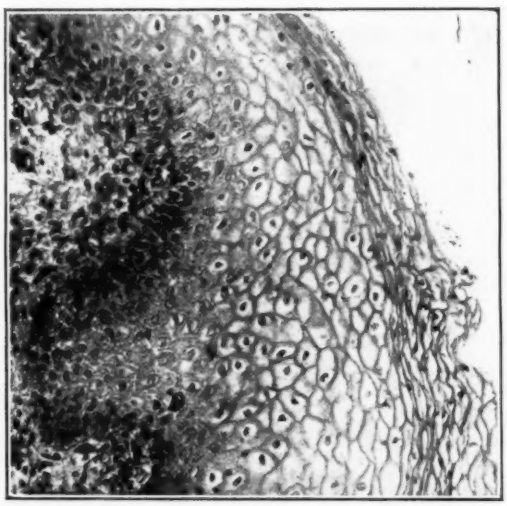

Fig. 3.—Vaginal wall of child aged eight months after injections of theelin, 100 R.U. daily for ten days, total 1,000 R.U. Here the mucosa resembles that of the newborn child showing many layers of vacuolated, partly cornified or cornified squamous cells.

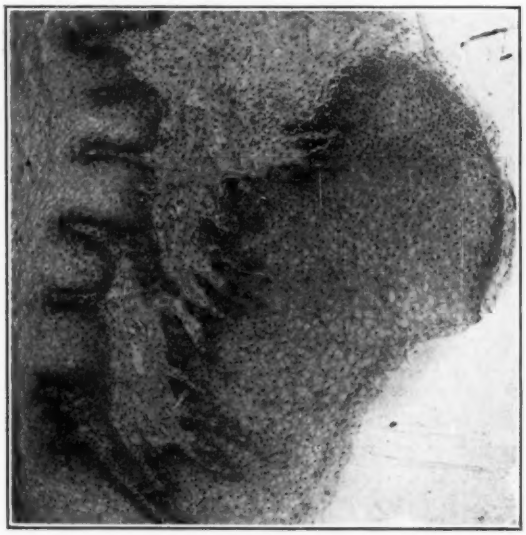

Fig. 4.—Vaginal mucosa of woman seven months pregnant. Specimen taken from a series studied with Dr. Herbert Thoms.

Hisaw[4] after reviewing the studies on the mucification of the vaginal mucosa of various rodents concludes, "these results very strongly indicate that theelin (in subthreshold doses) is either directly or indirectly responsible for vaginal mucification . . ." Probably the appearance of cells showing vacuolization in the human vagina is analogous to those showing mucification in the rat.

In passing it should be noted that the author's original article[3] has given rise to a slight misunderstanding. Commentators have arrived at the erroneous conclusion that theelin given to children produced an adult type of vagina. Quite the contrary is the case, the treated mucosa resembling that of the newborn infant.

Smith and Brunner[5] recently published an illuminating study on the structure of the vaginal mucosa in relation to the menstrual cycle and pregnancy. Studying a large number of biopsies taken from the normal adult vagina they made observations of great interest. In their conclusions they note that vacuolization of the cells of the basal zone beneath the zone of cornification is somewhat more marked in the premenstrual and postmenstrual periods than at other times in the menstrual cycle. I am at a loss to account for this by the presence in greater or lesser amounts of theelin during the different stages in the menstrual cycle. The

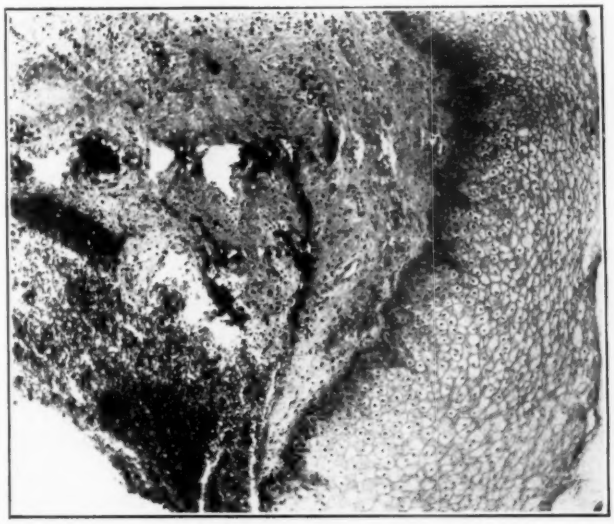

Fig. 5.—Vaginal mucosa at time of delivery from patient at term. Note many layers of vacuolated squamous cells in mucosa. The surface is somewhat fragmented. (Section given the author by Dr. Edgar Allen.)

authors of this study themselves state that "high and low points (of vacuolization) alternate in such a way that they seem unrelated to the menstrual cycle." The total averages of vacuolization in their series of cases vary between 2.11 at the time of menstruation to 2.71 in the postmenstrual period, a difference, but not a very marked one.

During pregnancy, when the amount of theelin is at its greatest over a long period, one would expect vacuolization of the basal cells if the presence of theelin is responsible for its appearance. Smith and Brunner state "we have found a high degree of vacuolization in the cells of the basal zone (of the vaginal mucosa) in every normal biopsy taken during pregnancy." Their reproductions of photomicrographs of specimens taken from women approximately six weeks and seven months pregnant are very striking in this respect.

Smith and Brunner state that their studies show a high degree of vacuolization of the vaginal mucosa during pathologic amenorrhea and after the menopause. To me, this would suggest that an excess of prolan or other hormone may have the

same effect in this respect as theelin. There is of course a likelihood that there is a close relationship in the chemical composition of these substances.

At the very end of pregnancy, soon after the high point of theelin in the maternal organism has passed, we would again expect marked vacuolization of the vaginal mucosa. Specimens of vaginal mucosa taken at the time of delivery show this condition to an extraordinary extent. Here we find (Fig. 5) a mucosa consisting of a basal zone of compact cells overlying a hyperemic submucosa with areas of extravasated blood and leucocytic infiltration. The deep zone of compact cells is usually from 4 to 6 layers in depth, these cells containing uniformly deep staining nuclei.

Overlying this is a series of remarkable layers of vacuolated cells, many of which contain nuclei in good condition, although some are pycnotic.

Superficially we find six to eight layers of more or less cornified flattened cells fragmented in some areas. The vacuolated cells and their arrangement again closely resemble those found in the vaginas of the newborn or in the specimens taken from children who have had a course of theelin injections. Again presumably the presence of theelin has been responsible for their production.

CONCLUSION

It seems evident that the presence of an excess of theelin (possibly also other hormones) in women produces vacuolization and multiplication of certain layers of cells in the vaginal mucosa. This vacuolization is strikingly evident in the newborn and in children injected with theelin. Biopsies of vaginal mucosa taken during pregnancy, when theelin is abundant, may show marked vacuolization on microscopic examination. In specimens taken at the time of delivery vacuolated cells in many layers are in evidence.

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52 Trumbull Street

RELATION OF VITAMIN B DEFICIENCY TO METABOLIC DISTURBANCES DURING PREGNANCY AND LACTATION*

EARL MENDUM TARR, M.D., AND OLGA MCNEILE, M.D.,
LOS ANGELES, CALIF.

IN OUR earlier studies† it was found that the average American dietary is deficient in vitamins; especially the B complex. Studies I, II, and III of this series confirm the opinions of many observers.[1, 2, 3, 4, 5, 6, 7, 8] In study IV it was shown that infants subsisting entirely upon a milk diet often show signs of vitamin B deficiency.[9] To what extent the diets of infants and of adults must be supplemented with the B complex has been, and still remains, a matter of debate among clinicians as well as among biochemists. With our ever broadening knowledge of the quantitative distribution of the several known vitamins in common foodstuffs, we find ourselves approaching, perhaps, the solution of some of the baffling phases of the entire field of vitamin requirements.

For the busy physician to do more than scan nutritional abstracts is impossible. New journals dealing almost entirely with problems of nutrition are announced with regular frequency, and a maze of conflicting theories are being brought forth. However, out of a maze of laboratory investigations we have at least culled a few practical points. It has at last been definitely shown that while vitamin B is widely distributed in the articles which enter into the usual dietary, the actual amounts available of this vitamin complex are much less than was our belief a few months ago.

Indeed, it is doubtful if one in ten adults obtains an adequate amount of the B complex in what may be called the standard diet. The same no doubt holds true for infants who subsist entirely, or almost entirely, upon a milk diet.

In order that we may proceed intelligently with a study of this character it is necessary to know:

a. Some of the signs of vitamin B deficiency.[10, 11, 12, 13]

b. The quantity of the B complex which must be taken daily to constitute adequacy.[14, 15, 16, 17]

c. The foodstuffs which, when consumed in sufficient amounts, will provide that which we seek.

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*Read before the Riverside County Medical Society, October 14, 1933.

†This and other studies in the series were made possible by a grant from Mead Johnson & Company. Animal experimentation conducted at the University of California.

SIGNS OF VITAMIN B DEFICIENCY

The symptoms of advanced deficiency disease need not be enlarged upon. Polyneuritis and pellagra are examples of prolonged vitamin B starvation. Both diseases are sufficiently well understood to make diagnosis fairly simple. The early signs of inadequacy—those which make their appearance before gross pathologic changes take place—are the signs with which we should be familiar. They may be mentioned in the order of their appearance, both in adults and in children, as follows:

1. Impairment of the digestive function—either mild or severe. One of the most severe manifestations is actual cessation of digestion.
2. Intestinal stasis; due to diminished neuromuscular control of the intestine.
3. Loss of appetite (often the first symptom for which relief is sought).
4. Constipation.
5. Restlessness.

Knowing that one or more of these symptoms are mentioned in over half of all new case histories it may be reasonable to assume, in the case of the pregnant woman, that vitamin B deficiency must be considered.

WHAT AMOUNT OF VITAMIN B COMPLEX CONSTITUTES ADEQUACY?

In man, as well as in the experimental animal (rat), it has been shown[18, 19] that the best condition of health and nutrition requires that the food furnish much more of this vitamin complex than is needed to sustain normal growth. The actual number of B complex units necessary to sustain normal growth in an infant, in a five-, and in a ten-year-old child may vary inversally with the age-change. It has been shown, however, that for practical purposes we may expect 300 units to meet the growth requirements for an infant under one year. Optimum requirements are at least 25 per cent higher. From the sixth to the sixteenth year the optimum growth and maintenance requirements seem to be greatest; from 500 to 700 units being necessary. The unit of vitamin B complex, as used in this study, is that amount which when fed as a daily allowance to a standard rat results in net maintenance over an eight-week period.

To help determine the number of units which may be regarded as safe we have taken as a starting point, clinically, a study of the dietary of several hundred pregnant women. The vitamin B units are determined. Symptoms of deficiency disease are scrutinized and evaluated. The diet is supplemented with increasing amounts of vitamin concentrate or foods known to be rich in this vitamin. When symptoms of deficiency disappear the number of B complex units taken daily are estimated and this number is regarded as minimum for the individual. Hundreds of such tabulations have given the figures upon which some of our contentions are based.

Being aware that the early signs of de-mineralization, both in the infant and in the pregnant woman, closely simulate the early signs of vitamin B deficiency; and being aware that marked de-mineralization usually, if not always, accompanies and follows pregnancy, this study was undertaken with the hope that we might determine whether and to

TABLE I. FOODSTUFFS KNOWN TO CONTAIN THE VITAMIN B COMPLEX

Vitamin B (B1) Antineuritic anti-beriberi		
Artificial Concentrates: Yeast, rice polishings, wheat germs.		
Most potent source:	Plant	Animal
	Yeast	None
Excellent source:		
Plant:	Cereals, whole wheat, corn, rice, oats, wheat bran.	
Animal:	Egg (yolk)	
Good source:		
Plant:	(Vegetables)	Asparagus, bean, cabbage, carrot, celery, collard, cauliflower, lettuce, onion, parsnip, potato, tomato, spinach, turnip, watercress.
	(Fruits)	Apple, banana, cantaloupe, date, grape, grapefruit, lemon, orange, peach, pineapple, prune, strawberry, nuts.
Animal:		Brain, cheese, kidney, liver, milk, oysters (raw)
Vitamin B (B2) Antipellagric		
Artificial concentrates: yeast		
Most potent source:		
Plant:	Yeast.	
Animal:	Glandular organs, liver, kidney, spleen, lean meat.	
Excellent source:		
Plant:	Beet greens, kale, potato, spinach, turnip, watercress, wheat germ.	
Animal:	Egg, haddock, salmon, milk.	
Good source:		
Plant:	Banana, beet, cabbage, carrot, cowpea, lettuce, onion, tomato, turnip, greens, wheat bran.	
Animal:	None.	

what extent the diet of many pregnant women might be found inadequate as regards both the vitamin B complex and mineral intake, especially calcium and phosphorus.

It should be remembered that "averages" like "norms" are variable. What may actually be adequate for one individual cannot be held as adequate for all other individuals. Nor should it be assumed that the metabolic processes of a laboratory animal at all times and under all conditions duplicate the metabolic behavior of man. It may, however, be assumed with more or less safety, that the studied behavior of an experimental animal on a deficiency diet may throw light upon the cause of some of the common deficiency disorders to which man is subject.

In former studies several bits of evidence were collected which pointed toward the possibility of deficiency intake of the vitamin B complex in the dietary regimen during pregnancy and lactation. For several years it has been our belief that during pregnancy and lactation, at least 40 per cent of the total calories should be derived from the protective

foods. Analysis of the dietary of several hundred women during these periods has shown that few, if any, of them get more than 12 to 15 per cent of their calories from protective foods. This study, then, also served as a test of our theory in this matter.

METHOD OF PROCEDURE

Two diet forms were prepared. The items were identical on both sheets. Those women who served as controls were advised to adhere to the articles of food named on the sheet. The actual amounts of food to be eaten were left entirely to their discretion. This seems to be the prevailing custom with many physicians, not excluding all of those who limit their work to obstetrics.

Those women who were to serve as test cases were given the same food list but, in addition, definite amounts of all food items were specified for them, and they were requested to live up to these specifications. The cereals advised were those known to be rich in minerals and in the B complex. In certain selected cases a mineral mixture containing iron, phosphorus, calcium, magnesium, sodium, and potassium was advised. This mixture was suggested to those women who, during previous pregnancies, were known to suffer serious demineralization.

TABLE II. FOOD CHART AS A GUIDE TO CONTROL AND TEST CASES

Cereals:	Mead's cereal,* cracked wheat, yellow corn meal, wheat bran, oats.
Fruits:	Apple, banana, cantaloupe, date, grape, grapefruit, lemon, orange, peach, pineapple, prune, strawberry. Also juice from these fruits.
Vegetables:	Asparagus, beans (all kinds), cabbage, carrot, celery, collard, cauliflower, lettuce, onion, parsnip, potato, tomato, spinach, turnip, cowpea, watercress, kale, beet and turnip greens, calavo.
Meat and Fish:	Haddock, whitefish, salmon, lean beef (steak, roast, ground chuck), brain, kidney, liver, bacon, lamb chop, squab and chicken.
Other Foods:	Egg, oyster (raw), milk, cheese, butter, cream, toasted bread, nuts, oil dressings. Tea, coffee, and beer were not denied.
	Suggestions for One Day (Control Cases)
Breakfast:	Fruit juice, stewed fruit, egg, bacon, toast, cereal, milk or coffee.
Luncheon:	Lettuce or tomato (or combination) salad with oil dressing; portion of two green vegetables, fruit, milk, crackers or toast.
Dinner:	Serving of meat or fish; serving of at least two green vegetables; bread and butter, cheese or calavo or nuts, milk or coffee.

It has been observed by several collaborators that most pregnant women, with such a food list as a guide, will consume from 1,600 to 1,900 calories daily. By careful checking it is found that they obtain, as a rule, less than 15 per cent of their calories from the protective foods on the list. The study shows that the three meals are made up something after the following fashion:

Breakfast: Small glass fruit juice (4 ounces); small dish cereal (1 to 2 small tablespoonfuls); one piece toast, one piece bacon; one cup coffee with cream and sugar.

Luncheon: Meat or vegetable sandwich; baked apple, cup of tea or glass of milk (4 to 6 ounces).

Dinner: Medium to small sized serving of meat or fish; one tablespoonful each of two cooked vegetables; one tablespoonful fruit or vegetable salad; one slice bread or toast; cup of tea or glass of milk (4 to 6 ounces).

*A wheat germ cereal rich in calciums, phosphorus, sodium and potassium—now named "Pablum."

By referring to almost any table of food values it is discovered that such a breakfast supplies about 75 to 85 per cent of the calories from the nonprotective foods. About the same ratio holds true for luncheon and dinner.

The wisdom of such dietary imbalance must be challenged. Laboratory animals fed on a B complex deficient diet may be depended upon to perform in a definite manner. Litters are dropped prematurely. Only a few survive unless something is done. When sufficient amount of the B complex is fed to these weaklings, most of them immediately show signs of improvement. If the treated members of the litter survive and thrive and the untreated promptly die, it may be assumed that inadequacy of the B complex was, in some measure at least, the cause of the prematurity and the death of the young. Hundreds of litters of albino rats have been studied and the fate of the young not only observed but also predicted.

On the reverse side of the "Food Chart" handed to our test cases was outlined the amounts of various foods necessary to provide a certain number of B complex units (Table III).

TABLE III

	CALORIES	PROTECTIVE VIT. B	NON-PROTECTIVE
Breakfast:			
8 ounces fruit juice	100	76	--
4 ounces fruit pulp	45	48	--
1 egg	82	30	--
1 slice bacon	40	--	40
½ ounce butter	95	--	95
8 ounces milk	156	70	--
1 slice toast	15	--	15
	533	224	150
Luncheon:			
½ head lettuce	22	35	--
1 ounce oil dressing	182	--	182
3 ounces fresh vegetable	155	162	--
½ ounce butter	95	--	95
1 slice toast	15	--	15
4 ounces fresh fruit	40	48	--
8 ounces milk	156	70	--
	665	315	292
Dinner:			
4 ounces meat or fish	175	?	175
2 ounces creamed spinach	120	65	--
2 ounces other green veg.	112	125	--
½ ounce butter	95	--	95
1 slice rye crisp (3 × 3)	20	--	20
4 ripe olives (med.)	27	16	--
1 ounce cheese	45	--	45
½ ounce nuts or raisins	50	150	--
8 ounces milk	156	70	--
	800	426	335

It has been found that, with such a brief outline, many women can, over a period of weeks, vary their meals in a most satisfactory manner.

It will be observed that such a combination of foods supplied about 2,000 (1,998) calories daily, and that the B complex units amount to 965; not quite 50 per cent of the total calories. Brewer's yeast,* two teaspoonfuls daily, supplies about

*Refers to vitamin B and mineral preparations manufactured by Mead Johnson & Company.

400 units and this amount was advised for all patients who were disturbed by gas or constipation. In other words, our test cases all received considerably more than 50 per cent of their calories from protective foods; some of them as high as 75 or 80 per cent.

RESULTS

Time will not permit a detailed explanation of the results of the test. A summary of the findings show several interesting things (Table IV).

TABLE IV. CONTROL GROUP

Deliveries 116 (Primiparas 47; Multiparas 69)		
Low forceps 8, Section 1; Version 1, normal 108		
Blood picture (first) Average: Hg 72%; R.B.C. 3,600,000; W.B.C. 8,200		
Taken day of delivery: Average: Hg 70%; R.B.C. 3,800,000; W.B.C. 8,750		
Incidence digestive impairment: Mild 36, moderate 8, severe 4		(38%)
Loss of appetite: Before sixteenth week 5, thereafter 9		(12%)
Intestinal stasis and constipation:		
Primiparas: Mild, 6, moderate 4, severe 16		(55%)
Multiparas: Mild 22, moderate 15, severe 12		(70%)
Headaches of vague origin (Blood pressure normal)		
Primiparas: 15		(30%)
Multiparas: 17		(24%)
Hemorrhage following delivery		
Low forceps 2		
Normal delivery 6		(6½%)
(By hemorrhage was meant the loss of sufficient blood during or following delivery to produce clinical signs as pallor, changes in pulse, signs of shock, etc. Blood picture changes not taken into consideration.)		
Lactating Ability		
Adequate supply for 12 weeks	80	(69%)
Adequate supply for 16 weeks	59	(51%)
Adequate supply for 20 weeks	37	(32%)
Adequate supply for 24 weeks	17	(15%)
Adequate supply for 30 weeks	9	(8½%)

The physical, mental, and emotional status of these women was considered. A rough estimate would declare about half of them in rather good general condition during pregnancy and during the lactation period. A number of them were victims of marked irritability and emotional instability during pregnancy. Most of these women were more unstable during their lactating period than during their pregnancy. As many as 10 per cent were regarded to be in fair to poor physical condition during the time they were under observation. Constipation and starvation stools were two outstanding problems with many of the group.

The physical, mental and emotional status of this group of women was considered and discussed. That, as a group, they were more satisfactory patients was the unanimous opinion. With but two or three exceptions they all reached their delivery dates in satisfactory condition. Many of the usual annoyances so often encountered during the lying-in period were conspicuous by their absence. Supervisors in the obstetric department of several of the hospitals reported good appetite, freedom from breast complications, and a much healthier and happier frame of

mind in these women than in the control group. In fairness it must be said that the state of mind of the test group was allowed to occupy a prominent place in their management. All of them, particularly the primiparas, were imbued with the idea that most of their fears were groundless; they were all encouraged to live considerably "outside of

TABLE V. TEST GROUP

Deliveries: 120 (Primiparas 60, Multiparas 60)		
Low forceps: 12, Section 3, Normal 105		
Blood picture (first) Average for group:		
Hg 75%; R.B.C. 3,750,000; W.B.C. 8,750		
Blood picture (just before delivery) Average:		
Hg 85%; R.B.C. 4,800,000; W.B.C. 11,200		
Incidence digestive impairment: Mild 18, moderate 6, severe 1		(20%)
Loss of appetite: Before sixteenth week 3, thereafter 4		(6%)
Intestinal stasis and constipation:		
Primiparas: Mild 4, moderate 7, severe: none		(18%)
Multiparas: Mild 15, moderate 8, severe: 1		(40%)
Headache of vague origin (Blood pressure normal)		
Primiparas: 4		(6⅔%)
Multiparas: 2		(3¼%)
Hemorrhage following delivery: 2		(3⅓%)
(Loss of sufficient blood to produce clinical signs such as pallor, changes in pulse, signs of shock, etc.)		
Lactating Ability		
Adequate supply for 12 weeks	94	(78%)
Adequate supply for 16 weeks	91	(74%)
Adequate supply for 20 weeks	78	(65%)
Adequate supply for 24 weeks	45	(37%)
Adequate supply for 30 weeks	22	(18%)

themselves." We do not mean to say that the control group was slighted in this respect, but more interest was developed in the test group. A more satisfactory and interesting relationship existed between this group and their physicians.

IMPRESSIONS

We believe that vitamin B deficiency in the diet of pregnant and lactating women usually produces definite symptoms. Signs of demineralization are more pronounced in those women who obtain less than 50 per cent of their total calories from protective foods. The physical and mental health of man depends largely upon a normal blood picture and a normal ability to assimilate food. In this study it was observed that our test cases showed a much better blood picture than was true with the controls. While the matter of miscarriage has not been considered in this study, yet it is a matter of record that 5, or 4½ per cent, of the control group were threatened with this accident.

The test group escaped all such symptoms and, while this proves nothing, we may ultimately discover that dietary imbalance and poor assimilation may play a part in the etiology of some of these unexplainable accidents.

More calm and better milk producers were found in the test group. Severe signs of gastric and intestinal atony were almost entirely absent in the test group whereas in the control group these signs were met with in over 20 per cent of cases. We do not believe that this was purely coincidental. Previous views concerning some of the signs of vitamin B deficiency during pregnancy and lactation have been substantiated and strengthened. Vitamin B and mineral preparations used in this study were found to be satisfactory and reliable.

More infants should be breast fed; and for a longer period. The lactating ability of the mother rests very largely with the obstetrician rather than with the pediatrician. Most mothers cooperate satisfactorily if and when they are under adequate prenatal medical supervision. The surest method of weaning an infant is to insist that supplemental or complemental feedings be given so that the child will have regained its birth weight before leaving the hospital on the tenth to fourteenth day.

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During the years 1922 to 1931, inclusive, there were 8,346 mothers delivered at the Frauenklinik of the University of Innsbruck. Of these, 45 per cent were primigravidas and the rest were multigravidas. To these mothers were born 8,425 children more than 1,500 gm. in weight and 35 cm. in length. There were 38 maternal deaths and 335 fetal deaths, incidences of 0.45 and 3.99 per cent, respectively. There were 861 operations, excluding episiotomy, 10.3 per cent, distributed as follows:

OPERATION	NUMBER PERFORMED	PER CENT OF TOTAL NUMBER OF LABORS
Forceps	165	1.97
Version	113	1.35
Cesarean section	68	0.81
Manual dilatation of the cervix	51	0.61
Cervical incision and vaginal section	25	0.30
Embryotomy	30	0.36

There were 578 episiotomies performed, making a percentage of 6.94.

WILLIAM F. MENGERT.

A STUDY OF THE COLLAGEN OF THE PLACENTA

BENJAMIN TENNEY, JR., M.D., F.A.C.S., BOSTON, MASS.
(From the Gynecological and Obstetrical Service of the Boston City Hospital)

THE purpose of this work has been to trace the development of collagen in the different parts of the placenta, the development of the basement membrane of the villi, and the relation of the above to nephritis, preeclamptic toxemia, and eclampsia. Also it has been interesting to observe the relation of the collagen formation to the development of chorionepithelioma. A series of placentas of varying ages have been fixed in Zenker's solution, and then stained by the Lee-Brown modification of Mallory's connective tissue stain. Also a few specimens of chorionepithelioma have been similarily treated.

In using the term "collagen" I am referring to a substance that stains dark blue with the connective tissue stain. Of course this stain is not specific. It also stains amyloid and other hyaline-like substances. However, I believe it to be true collagen as it is definitely not the result of an inflammatory process and also fibroglia can be demonstrated by the phosphotungstic acid stain on the cells that lie in the midst of this substance.

In early villi of two months' age, the loose stroma of the villi contains very few fine collagen fibers. There is no collagen in or around Langhans' layer and none in the syncytium. Large cell islands of trophoblasts that have not come in contact with maternal cells show a few very fine collagen threads. Wherever the trophoblases come in contact with decidua, however, there is a fairly dense layer of collagen laid down (Fig. 1). It is also of interest to note that in the decidua itself there are only a few fine threads of collagen present. In the decidua vera there is practically no collagen. Therefore, it takes the contact of the fetal and maternal cells to stimulate the formation of collagen. A case of three months' pregnancy, where a hysterectomy was done because of a very large fibroid, shows a definite placenta accreta. There is practically no decidua present and the villi are firmly fastened to the uterine muscle. In this case there is a marked absence of collagen formation similar to that of the chorionepithelioma. It is a similar process except that the trophoblast cells have not acquired malignant characteristics.

In the specimens of tubal pregnancy (Fig. 2), except for occasional decidua-like cells in the tubal walls, there is no real decidual reaction

or defense against the invasion of the fetal cells. The result is large masses of trophoblasts containing very little collagen advancing through the muscle layers of the tubal wall to inevitable rupture if tubal abortion does not take place. There is here some defense reaction of the fibroblasts of the tubal wall in the formation of collagen, but it is not marked and entirely ineffective. Here as in placenta accreta the fetal cells show no malignant characteristics except their local invasive power. It does seem remarkable with the fetal cells spilled in the abdominal cavity and on the neighboring organs that there are no secondary growths. This again emphasizes the fact that the fetal cells do not grow outside of their own milieu unless they

Fig. 1.

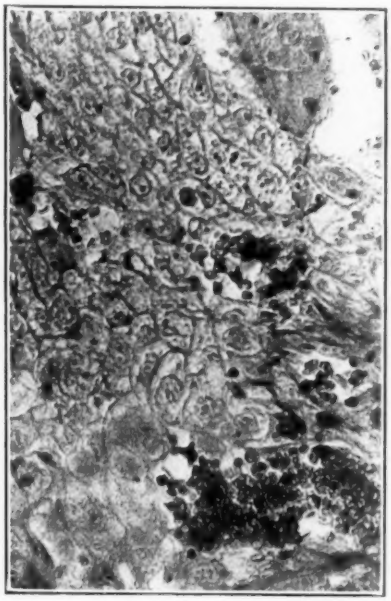

Fig. 2.

Fig. 1.—Section showing invasion of trophoblast cells above. Note dense collagen around cells. In center is considerable destruction where maternal and fetal cells meet with blood clot and collagen. Below to right decidual cells. ×400.

Fig. 2.—This section shows mass of fetal trophoblast invading tubal wall in tubal pregnancy. Note lack of collagen around trophoblast cells. ×400.

have assumed malignant characteristics. The frequent finding of fetal cells in the lungs of normal pregnancies, carried there by the blood stream, and yet showing no signs of implantation or growth is proof of this point. Another point of interest in tubal pregnancy is the examination of the uterine decidua. The uterine decidua although well formed of typical decidual cells, is practically free of any collagen formation. There are a few fine collagen fibers present but without the presence of fetal cells the formation of collagen is practically absent.

The most extreme example of lack of collagen formation is found in studying various sections of chorionepithelioma, the invading cells of which consist of fetal trophoblasts that have assumed malignant characteristics (Fig. 3). These can be seen invading the entire uterine wall. In the first place there are large masses of fairly typical trophoblast cells invading the inner part of the uterine wall. There is a marked absence of collagen in these cell masses. In other words, although they have invaded the uterine wall, they appear similar to the early trophoblast of normal pregnancy that have not come in contact with maternal tissue. Around the edge of these invading masses is

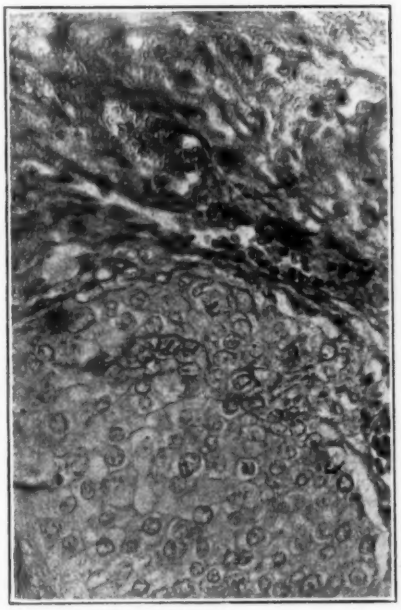

Fig. 3.

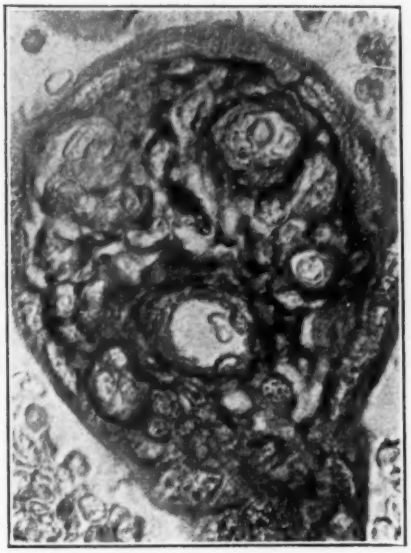

Fig. 4.

Fig. 3.—A section of chorionepithelioma invading uterine wall. Note lack of collagen around invading cells as well as very thin layer of collagen around border. ×400.

Fig. 4.—A normal full-term placenta showing characteristic basement membrane beneath syncytium. ×1000.

a very thin line of collagen. Second, there are long thin columns of deeper invading trophoblast cells that are actually destroying such collagen as is present in normal uterine stroma. Third, the invasion of scattered trophoblastic cells throughout the entire uterine wall shows a markedly phagocytic action in regard to collagen as well as uterine muscle. The entire uterine wall shows the normal collagen of its connective tissue stroma or the remains of it, but no defense reaction of collagen formation. There is no definite contact layer between fetal and maternal cells and no maternal reaction to the fetal

invasion. This is the same as saying there is no decidual reaction as there is no sign of any decidua present.

In the middle of pregnancy, four and a half to five months, there is a definite increase in the amount of collagen throughout the placenta. The stroma of the villi shows heavier collagen fibers. Around the early blood vessels there is a fairly thick layer of collagen already formed. Beneath the Langhans' layer that is disappearing rapidly there is a faint line of collagen between it and the stroma. This is the beginning basement membrane that will be taken up in more detail later. The syncytium itself shows no collagen formation. Most of the trophoblast cell islands have come in contact with maternal tissue and show considerable collagen in and about the cells. However, there are some islands still to be found without much collagen formation. The septa of the placenta at this stage already show a marked invasion by trophoblast and destruction of decidual cells. The stain used in this work shows a good differentiation between trophoblast and decidual cells. The trophoblast cells have a more granular cytoplasm, more irregular nuclei and stain a brighter yellow. The decidual cells have a homogeneous almost milky cytoplasm, clear cell outline and distinct round nuclei, and do not stain as brightly as the trophoblast cells. In the replacement of the decidual cells in the septa by trophoblast invasion, there is a dense collagen formation wherever the trophoblast cells have invaded, and this increases with the age of the placenta. The contact zone of maternal and fetal cells or the "Durchdringungzone" of Grosser[2] already shows a well-formed and fairly thick layer of collagen formation. The actual villi do not advance beyond this layer as a rule, although there are many trophoblast cells and many nucleated giant cells advancing beyond this into the compact layer of the decidua and even into the muscle. The compact layer of decidua at this period is still fairly broad and intact although the decidual cells have become somewhat flattened. There are some areas of collagen around the fetal cells that have invaded this decidua but as a whole it contains very little collagen.

At term the stroma of the villi is practically replaced by blood vessels which have a very thick surrounding layer of collagen. The Langhans' cells are largely absent and the syncytium contains no collagen. The syncytial buds both free and attached to villi show no collagen formation.

On the maternal side of Nitabuch's layer there are masses of cells surrounded individually by considerable collagen. There are large numbers of these cells in most placentas although there seem to be more in some than in others. They are quite large and stain bright yellow. They can be seen extending up the septa in large masses with

much collagen. Some are markedly degenerated and participate in small cystic formations. External to these cells is a thin layer of separated flattened cells with very little collagen. This thin layer of cells is in all stages of degeneration and is most likely composed of remaining decidual cells. As to the origin of the collagen or of the cells imbedded in it on the maternal side of the placenta, I do not feel that it can be definitely stated. The cells may be forming the collagen themselves, or it may have been formed by the degenerating decidual cells previous to their degeneration. I am inclined to think that these cells are fetal in origin for two reasons. In the first place the collagen surrounding them is not formed in decidua unless fetal cells are present. In the second place these cells show definite fibroglia with the phosphotungstic stain, while I have not been able to demonstrate fibroglia in true decidual cells.

In the study of the collagen of the placenta, it has been of special interest to trace the development of the basement membrane of the villous epithelium. This was described by Bonnet[3] in 1903. A definite basement membrane (Fig. 4) can be found in all ripe placentas, although it is hard to demonstrate in some villi, apparently due to the way they are cut. The beginning of the basement membrane can be clearly seen in some villi previous to the disappearance of Langhans' layer. When seen in these specimens, it lies between the villous stroma and Langhans' layer. Although the basement membrane becomes thicker and more distinct as the Langhans' layer disappears, its original position inside Langhans' layer would make it appear to have been formed by the fibroblasts of the villous stroma[4] rather than be a result of the degeneration of Langhans' cells. As the placenta grows older this basement membrane becomes more and more distinct until at term it is a very definite layer. This membrane has a definite thickness and staining reaction that is quite characteristic. Even in the old fibrotic type of placenta where the villi are small and with the Lee-Brown stain appear to be almost entirely filled with collagen, the basement membrane does not thicken in proportion. It is of interest when one considers the similarity of function between the villus of the placenta and the glomerulus of the kidney that each has a capillary bed surrounded by epithelium and a basement membrane.[5] Bell[6] has described as the typical lesion in the eclamptic kidney the thickening of the basement membrane of the capillaries of the glomerulus. With this in mind I studied the basement membrane in eclampsia, preeclamptic toxemia, and nephritis. In eclampsia I found a definite thickening of the basement membrane of the villi (Fig. 5). This appears in large groups of villi spread throughout the placenta mixed with other areas of villi where the thickening of the basement membrane is not definite. This thickening of the basement membrane

seems definitely to be due to an increased number of collagen fibers. It has a homogeneous appearance, but in certain areas separate and individual fibers can be made out. The thickening is not uniform as some parts of a given membrane are much thicker and denser than the rest. The irregular pointed projections of the membrane between the syncytial cells seem to be more marked. These projections appear more prominent and denser just beneath areas of marked proliferation of the syncytial cells. In certain severe preeclamptic toxemias similar although fewer groups of villi with thickened membranes are found (Fig. 6). In many milder toxemias no definite change in the membrane is found. In chronic nephritis no definite change in the membrane could be made out. Therefore, it would seem as if in

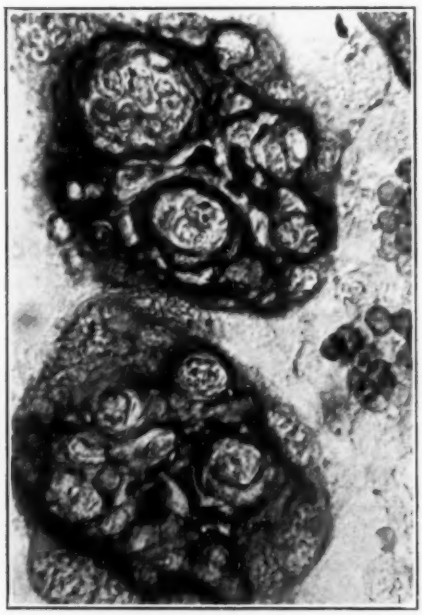

Fig. 5.

Fig. 6.

Fig. 5.—Villi from placenta of case of definite eclampsia at eight and one-half months' pregnancy. Note marked thickening of basement membrane. This placenta showed large areas of the above type of villi with some areas of normal appearing villi. ×1000.

Fig. 6.—Villous from a case of severe preeclamptic toxemia in an eighteen-year-old girl. A cesarean section was done to avoid impending eclampsia. Placenta showed numerous areas of villi with thickened basement membrane as above. ×1000.

eclampsia and severe preeclamptic toxemia, there is a definite thickening of the basement membrane of the villi which undoubtedly affects its permeability and powers of excretion and secretion.[7] This should not be confused with the thickening of the walls of the blood vessels in the physiologic endarteritis of the ripe placenta or the increase of the collagen of the stroma in old fibrous villi. It is the actual thickness of the basement membrane itself irrespective of the total amount of collagen in a given villus.

SUMMARY

A study of placentas of varying ages has been made. The Lee-Brown modification of Mallory's connective tissue stain has been used. The purpose has been to trace the development of collagen. The formation of collagen has been shown to take place at the junction of the fetal and maternal cells. It is not formed in decidua where there are no fetal cells. There is a marked absence of collagen formation in placenta accreta, in tubal pregnancy, and in chorionepithelioma.

A definite basement membrane of the villous epithelium has been demonstrated in the latter half of pregnancy. This has a definite width and thickness according to the age of the placenta. In cases of eclampsia and severe preeclamptic toxemia, a definite thickening of the basement membrane has been demonstrated which is not found in the normal ripe placenta, in nephritis, or in mild toxemias.

CONCLUSIONS

1. The formation of collagen around the fetal cells invading the decidua has been shown to take place in the normal development of the placenta. In certain abnormal conditions of the placenta this process breaks down.

2. The basement membrane of the villous epithelium can be clearly demonstrated by the Lee-Brown connective tissue stain in the latter half of pregnancy.

3. There appears to be a thickening of the basement membrane of the villi in eclampsia and in severe preeclamptic toxemia.

I wish to express my indebtedness to the Mallory Institute of Pathology for their assistance in this work.

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309 Marlborough Street

UPPER URINARY TRACT INFECTIONS COMPLICATING PREGNANCY*

HERBERT F. TRAUT, M.D., AND ALBERTA KUDER, M.S., NEW YORK, N. Y.
(From the Department of Obstetrics and Gynecology, Cornell University Medical College and New York Hospital)

IN THIS paper we shall present some of the deductions which study of the female urinary tract in pregnancy, as well as the literature upon the subject, have allowed us to draw. We intend to deal with the normal changes in the urinary tract accompanying pregnancy, and shall attempt to show how these alterations predispose the woman to disease. In addition, we shall consider the pathologic processes that may ensue with some evaluation of their meaning to the woman, and shall hope to be able to indicate sound physiologic principles for combating them.

If we regard pregnancy in the woman simply as a biologic process, we find it in most respects admirably adapted to its purpose, but in others, either it is still in process of adaptation, or orthogenetic influences have brought about changes which are definitely deleterious to its purpose. By orthogenesis we mean that tendency in evolution which permits continued development in a given direction even though it be harmful to the species. Genealogic examples of this are the saber-toothed tiger whose maxillary equipment developed to such a remarkable degree that what was once a formidable armamentarium for attacking its prey became, finally, a hopeless impediment and was the most important factor in the extermination of the species. Other examples are the mammoth with its huge curving tusks, the Irish stag with its magnificent spread of antlers of over six feet, as well as many of the reptilia. From the studies of Grosser it seems very probable that certain of the developments of the human placenta, particularly the retardation of the rate of blood circulation, may be regarded as an example of the operation of this principle in the human species. It is possible that some of the toxemias as well, represent imperfections in adaptation of this biologic process to its environment. Whatever the true interpretation of these maladjustments or maladaptations may be, one comes to the conclusion that there are definite flaws in the process. One of these would seem to be our immediate concern in considering the cause of upper urinary tract disturbances in the pregnant woman.

*Read before the Academy of Medicine, Binghamton, N. Y., November 20, 1934.

First let us consider some of the advantageous variations which take place in the organs concerned. Many of the tissues of the pelvis undergo hyperplastic changes characteristic of pregnancy. The endometrium lining the uterus more than doubles its depth producing the decidua, the cervical glands penetrate the myocervix converting it into a soft, succulent structure, the connective tissue of the broad ligament proliferates, forming a protective mechanism against infection, and the musculature of the uterus, vagina, ureters, and bladder hypertrophy in preparation for the duties they will eventually perform. In addition, there is increased vascularity and hyperemia of all the pelvic organs. These are but a few instances of the profound morphologic changes that take place. In addition, there are physiologic variations. The uterus is converted by chemical or hormonal influences from a small, hard, muscular viscus into a large flabby sac which is markedly insensitive to stimulation until term is approached. Similarly, the large bowel and the ureter are somewhat atonic and sluggish in action. Whether or not the same physiologic factors affect atonicity in all these smooth muscle structures is not known. However, their somewhat similar reaction to pregnancy is suggestive. It is known that some of the chemical substances or hormones present in the blood in large quantity during pregnancy have a relaxing effect upon the musculature of the uterus and bowel. The work of Knaus, and Reynolds, among others, has demonstrated satisfactorily that the corpus luteum hormone, progestin, removes irritability from the smooth musculature of the uterus and makes it quite immune to many stimulating substances, such as pituitrin and adrenalin, which usually stimulate it to contraction. It is quite possible that the ureters and large bowel are somewhat similarly affected.

Other investigators, Westphal and Benda, have thought that this relaxation effect might be accounted for by the increased cholesterin circulating in the blood of the gravid woman. Still others, Stoeckel, Schumacher and Klaften, account for it in the general terms of "increatory intoxication."

Although the explanation may be somewhat in doubt, we have learned that the uterus, ureters, and large bowel undergo an atonic change, which commences during the early months of pregnancy and persists until the eighth month, when it slowly diminishes, so that at term the uterine musculature is not only irritable but contracts vigorously. We have observed much the same reaction in the ureter. As far as the uterus is concerned, this atony of the musculature is a beneficial physiologic phenomenon, being a safeguard against abortion, but in the ureter, as we shall see, it constitutes a hazard to the woman.

Since Cruveilhier and Sipple in 1843 described widely dilated ureters in the bodies of pregnant women upon whom they made postmortem

examinations, it has been suspected that there might be profound morphologic changes at work in these organs. However, not until the advent of the roentgenogram and safe contrast media, such as neoskiodan and sodium iodide, together with adequate technic for introducing them, has this suspicion become a certainty. We now know that moderate dilatation, elongation, and lateral displacement of the ureter, particularly upon the right side, are a normal concomitant of pregnancy in the woman in at least 80 per cent of the subjects studied, which now number in the thousands. In addition, there is frequently some dilatation of the renal pelvis and the left ureter. For many years attempts have been made to account for this phenomenon on the basis of the enlarged uterus with its contents, and the pressure they exert upon the pelvic brim. The fact that most of the widening of the ureter occurs above the linea terminalis and is seldom seen in the pelvic ureter is a strong point in support of this thesis. However, the fact that dilatation is frequently observed as early as the fourth month of pregnancy when the uterus is so small as not to be supposed to be capable of causing any considerable embarrassment, together with the observation that the dilatation is predominently right-sided, has tended, at least partially, to discredit this explanation as being adequate. Some observers, Halban being among the first, have called attention to the common dextrorotation of the gravid uterus, pointing out that such torsion exerts tension upon left-sided structures and tends to kink and exert pressure upon those of the right side. Others (Kretschmer and Hofbauer) have shown the marked hyperplastic changes in the musculature and connective tissue of the vesical trigone and ureter, and have postulated a narrowed lumen with urinary back pressure as the cause of the widening of the superior portions of the tract.

It seems fairly clear that, with the exception of atony, none of these factors operating alone can definitely be assigned as the cause of the ureteral dilatation characteristic of pregnancy, because we have similar forces caused by large ovarian cysts and myomatous uteri acting in the nonpregnant woman, in whom this ureteral picture is seldom observed. We must, therefore, seek some cause which is a constant occurrence in pregnancy. This seems to be the loss of irritability of the smooth musculature of the ureter and kidney pelvis. Atonic muscles plus the weight and torsion of the uterus would seem to account for the findings completely. The ureter in its relaxed state is unable to expel the urine secreted by the kidney because of the steadily increasing weight upon it as it crosses the pelvic brim; therefore, it gradually dilates and in doing so contains an increasing column of more or less static urine. In the normal woman the amount of residual urine in the ureter and kidney pelvis varies from 10 to 60 c.c., and

occasionally in those who have had rapidly repeated pregnancies this may amount to much more, even 200 c.c. Following delivery the ureter quickly recovers its tone and involutes much as does the uterus. This process is complete usually in about two months' time, so that pyeloureterograms taken after this interval show a normal outline.

Residual urine, whether it occurs in the bladder, ureter or kidney pelvis, is a source of danger which has long been recognized by urologists, as it is prone to infection and once contaminated, allows of such rapid growth of microorganisms as to make cure difficult as long as the stagnation persists. The pregnant woman with her dilated ureters is, therefore, in constant hazard of developing an upper urinary tract infection.

If, then, we accept what seems to be an inescapable conclusion, that the normal pregnant woman develops what borders upon a pathologic dilatation of the upper urinary tract as a result of the fundamental anatomical and physiologic features of the gravid state, the question may justly be asked why this has come about. In answer we are forced to speculate, and there are some facts in comparative biology which may be of assistance. In the first place, woman is the only mammal which assumes the erect posture as the chief position during waking hours. Others affecting it such as the kangaroo and chimpanzee, do so only partially with frequent reversion to the horizontal. In doing so, when pregnant, they remove the weight of the gravid uterus from the pelvis and its contents. So far as we have been able to discover woman is the only mammal in which the ureters become dilated in pregnancy. We may perhaps be justified in concluding, therefore, as woman elected to become more and more upright in posture, the weight of the uterus, when pregnant, also came to be more constantly borne by the bony pelvis. As far as the ureters are concerned this may have been an event which natural forces have not completely succeeded in compensating, placing it in the category of a maladjustment of these organs to the evolutionary changes of the race.

The mechanism whereby infection of the renal pelvis takes place is a mooted question. Some observers, Kretschmer and others, feel that there is regurgitation of purulent urine from the bladder into the ureter, postulating a decompensation of the ureterovesical valves. Despite interesting work done to prove this theory, it does not seem particularly convincing as an explanation of the usual mechanism, for cystitis is not a common antecedent of ureteritis. Others have demonstrated the passage of bacteria from the bowel by way of the lymphatics to the region of the capsule of the right kidney (Franke), and others have pointed out the relationship of the incidence of pyelitis to the existence of foci of infection in teeth, tonsils, sinuses,

appendices, and gallbladder. Because the *Bacillus coli* is the invading organism in over 90 per cent of the individuals suffering with pyelitis, the lymphogenous route would seem to be by far the most likely. It is a well-established fact that the kidney excretes bacteria. Crabtree and Dodds find the *B. coli* contaminating the urine in from 11 to 14 per cent of the many gravid women whose ureteral urine they cultured, while in the puerperium the bladder urine was infected in as many as 70 per cent.

With these facts in mind, it is remarkable that we see pyelitis gravidarum in as few as 2 per cent of our patients, the usually accepted incidence. One is forced to the conclusion that there must be protective forces at work. This seems to have been demonstrated by Dresel, who studied the opsonic index in pregnancy with regard to *B. coli* and learned that this measure of immunity is increased tremendously in normal women and, moreover, that it is low in those individuals who develop pyelitis.

The onset of the disease is usually after the fifth month of pregnancy, and not infrequently in the puerperium when it is likely to be mistaken for uterine infection. It is somewhat more common in primigravidae than in others. There is usually a dull aching pain in the right flank associated with fever, chills, sweating, malaise, and sometimes nausea or vomiting. Occasionally this is preceded by dysuria and hematuria, but often not. Examination reveals a tender kidney, sometimes enlarged, with tenderness in the costovertebral angle and over the course of the ureter. The urine is cloudy and contains clumps of white blood cells and many bacteria. The latter are usually *B. coli* with sometimes a staphylococcus or streptococcus as a secondary invader. The temperature runs a hectic course with rises frequently accompanied by a chill. Blood culture done at this time seldom yields a growth of organisms, although they must be present at least in small numbers in the blood stream since the picture is that of bacteriemia. The disease is accompanied by a marked tendency to secondary anemia, presumably because of the hemolytic propensities of *B. coli*. With proper therapeutic measures the course of the disease is brief as far as the clinical symptoms are concerned, but unfortunately the disease lurks in the tract throughout pregnancy once it develops. This observation has given rise to the dictum that pyeloureteritis is never cured in pregnancy, a statement which is not absolutely true, but is a safe point of view for the clinician to assume. Ordinarily after a few days the temperature falls and the acute phase is past. However, not infrequently in those with more marked infection or more complete obstruction, as well as in neglected cases, the symptoms and fever may persist, in which case we are usually dealing with an invasion of the parenchyma of the kidney and the disease

has developed into pyelonephritis with a much more grave prognosis. The involvement of the renal secretory tissue by inflammatory processes, particularly if bilateral, carries with it the dangers of uremia as an immediate threat, and cortical damage due to fibrosis with impaired kidney function as an ultimate possibility.

The pathologic picture of pyeloureteritis is one of peripheral inflammation of the walls of the ureter and renal pelvis in the earliest stages, with hyperemia and edema as the outstanding features. As the process develops there is an exudate formed covering the involved areas which tends to flake off and float in the urine; this is the source of the clumped pus cells so characteristic in the catheterized specimen. In addition, there is tremendous infiltration of the tissues with phagocytic cells of blood and connective tissue origin. When the process is prolonged these latter become organized into permanent scar tissue and thus fibrose the structures involved, impairing blood supply and mobility. When the dilated ureter becomes extensively involved in this inflammatory process it never involutes completely after the termination of pregnancy, but forms what the German clinicians speak of as the "fixed ureter of pregnancy." Herein lies one of the great dangers of pyelitis in pregnancy. The woman may be left with a tract or tracts that harbor large amounts of residual urine and possess little or no peristaltic activity. Such a patient is extremely hard to rid of infection, even though many months of careful treatment be lavished upon her. In other words, we may have chronic ureteritis and pyelitis as sequelae. These patients are particularly prone to a renewal of the acute phase in subsequent pregnancies.

As a more serious pathologic process in the acute phase, we may have extension of the inflammation from the pelvis of the kidney into the peripelvic tissues surrounding the large renal blood sinuses, with the added dangers of blood stream infection. On the other hand, the process may attack the medullary and even the cortical portions of the kidney, in which event these areas are rendered inactive due to edema and infiltration of inflammatory cellular elements. The process may go further and produce localized, cortical abscesses and even sepsis and death. In the past two years we have had three such events in an experience of about eight thousand pregnant patients. It is not this possibility, however, that should most impress us; it is rather upon the milder and more chronic sequelae, which are much more frequent and have a profound and lasting effect on the lives of many women, that we should seek to place the greatest emphasis.

The treatment of pyelitis divides itself into two phases: the first concerns the acute phase, and the second the chronic. The febrile patient should have complete rest in bed, bland diet, a fluid intake of 5,000 c.c. per day, adequate saline catharsis, alkalies such as sodium

bicarbonate 2 gm. t.i.d., and frequent change of position. On this treatment a large proportion of patients will become afebrile in a few days with complete disappearance of symptoms. However, they should remain in bed a full week after the temperature has become normal. This improvement seldom means that the patient is cured, particularly if it is antepartum, as repeated urine examination will usually show a continuance of pus and bacteria. From this time onward, if there be no acute exacerbation, the patient should be considered as chronically infected, bearing in mind the constant danger of a return of the febrile phase both ante- and postpartum. She should continue the therapy outlined above in a modified form until term with great emphasis upon the horizontal side positions as frequently as is possible. During the postpartum period she should be followed at fortnightly intervals with urine examinations. If she continues to pass pus and bacteria, the affected urinary tract must be treated by moderate dilatation of the ureter and lavage of the kidney pelvis preferably with normal saline solution. We have tried a large number of mild antiseptics for this purpose and have come to the conclusion that the mechanical flushing with the improved drainage resulting from dilatation are the essential factors in obtaining a good result and that antiseptics have little to offer. We feel that the dilatation of the ureter in these chronic infections is most important as the inflammatory thickening and fibrosis of the ureter tends to narrow the lumen and thus impede drainage. Fortunately, most patients under this treatment respond in a relatively short time; others, about 30 per cent, have a much more prolonged course, stretching out in some instances for months. It should not be necessary to point out the importance of protecting a chronically inflamed urinary tract from the embarrassment of further pregnancies. A smoldering infection in an atonic ureter will flare up with remarkable regularity in a subsequent pregnancy.

When the intermittent fever continues, as it does in pyelonephritis despite rigorous treatment, one must view the situation as most grave. This is particularly true, if the infection is bilateral and if there is evidence of retention, such as diminished urinary output and elevation of the nonprotein or urea nitrogen content of the blood stream. Under these circumstances, the uterus should be evacuated by the simplest and quickest means. The improved drainage resulting from release of pressure upon the ureters, as well as the decrease in waste products emptied into the maternal blood stream, serve as a source of great relief and may be the deciding factors in the patient's course. Whereas the forcing of fluids is an important feature in the treatment of pyeloureteritis, it must be used with caution in the patient suffering with extensive pyelonephritis because the ability of the kidney

to excrete water is diminished. For this reason, pelvic lavage through the ureteral catheter or the use of an indwelling catheter is far more important in these patients than we have found it to be in those suffering from pyeloureteritis. Other features of the patient's care are expectant. The chief differences between the two groups of patients, pyeloureteritis on one hand, and pyelonephritis on the other, is that the treatment of the former is conservative in the acute phase, with persistent and prolonged follow-up in the chronic, whereas, in the latter our therapy must necessarily be radical in a fair percentage of patients if the woman is to be saved from being a permanent invalid. The difficulty lies in the clinical differentiation of one group from the other. They are not clear-cut entities, but merge into one another. However, a few points may serve as guides. One should always be apprehensive about bilateral lesions, so much so, that if the temperature and symptoms do not yield after five or six days of active therapy, frequent blood chemistry examinations should be made to detect the first appearance of an elevation in nonprotein nitrogen. If a definite elevation occurs and persists in the absence of vomiting, one should not hesitate to terminate the pregnancy. That this will impress many as radical there can be no doubt; however, as a result of prolonged trial of conservative methods, the trend is definitely toward the prompt termination of pregnancy in this type of case.

What is the prognosis in women who have had a sufficiently severe inflammatory infection of the upper urinary tract as to cause the fever and symptoms of pyeloureteritis or pyelonephritis? It has not been possible to answer this question until comparatively recently. Through the excellent work of Klaften, Crabtree, Dodds, Prather and Kretschmer, to name only a few, who have followed their patients carefully in the postpartum months, we now know that previously we were much too sanguine as to the eventual outcome from the point of view of both baby and mother. In brief, approximately 50 per cent of these patients, speaking of pyeloureteritis, will after three months be completely well, and furthermore they will in all probability not have a recurrence in a subsequent pregnancy. About 33 per cent will harbor the infection for a longer period of time and show some degree of permanent damage to the tract, such as persistent dilatation with hydroureter and hydronephrosis of slight or moderate degree. The remaining 10 to 15 per cent show very definite hydronephrosis and renal damage as evidenced by decreased ability to excrete urea or phenolsulphonephthalein. In addition, we have learned that a certain percentage of febrile patients in the puerperium who have been regarded as suffering from a uterine infection have, instead, a urinary infection. The fetal mortality is usually found to be approximately twice as high in the pregnancies as is experienced in normal pregnancy.

The more severe sequelae of pyeloureteritis and pyelonephritis form a challenge to the obstetrician. They occur in the neglected patients in whom the condition has not been recognized or in whom proper treatment has not been carried out. We must learn how to diagnose and properly care for these important and far too frequent complications and sequelae of pregnancy. We recognize the importance of, and place a very proper emphasis upon the toxemias, but the urinary tract has been neglected. It is to be hoped that the future will show a very marked increase in appreciation of the significance of these lesions on the part of American obstetricians.

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THE PELVIC FASCIA*

A. Histologic Structure of the Planes of Tissue Used in the "Fascia Overlapping" Operation

B. An Attempt to Correlate Conflicting Views

Nathan P. Sears, Ph.B., M.D., Syracuse, N. Y.

(From the Department of Clinical Gynecology, Syracuse University)

BEFORE describing the pelvic fascia it is important to consider that within the abdominal and pelvic cavities there are two quite different systems of fascia. The one, a strong dense plane of true fascia lining the muscular and bony walls of the abdomen and pelvis, is designated as muscle fascia (Tandler),[1] deep intraabdominal fascia (Gallaudet),[2] or voluntary fascia (Davies).[3] From the abdomen it extends downward into the pelvis and at the origin of the levator ani muscle from the lateral pelvic wall it splits into three layers. One extends caudally to line the lateral wall of the ischiorectal space, the second covers the inferior surface of the levator and the third, the superior levator or supraanal fascia, covers the cranial surface of the levator and coccygeus muscles. The inferior and superior levator fascias meet at the genital hiatus and fuse around the free border of the levator muscle.

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The other, the subperitoneal connective tissue, so named by Tandler and called by Gallaudet the superficial intraabdominal fascia and by Daves the involuntary fascia, in the early development of the body is a loose areolar structure, which, as the organs of the pelvis are formed and move into their final positions, is developed into planes and bands which, from time to time have been given special names. This rather loosely woven connective tissue structure with its various condensed bands and planes fills the space between the peritoneum and the deep or muscle fascia lining the two great cavities. In some areas it is only a thin areolar substance, while in others it fills rather large spaces with compact bands of fibrous tissue, extending from the pelvic wall to the viscera.

One of these condensations is the Mackenrodt or cardinal ligament. This structure, considered by Mackenrodt to be an important support to the uterus, is described by Tandler as a condensation of the subperitoneal connective tissue about the uterine vessels as they approach the uterus. In my own dissections this structure was noted and found to be as described by Tandler. Koster[4] in histologic study confirms this opinion. He and Tandler state that because of its structure the cardinal ligament can be of no supportive or surgical importance. Davies although agreeing to its structure believes that it helps to support the uterus. To the writer, although it seems likely that even such loosely woven strands of connective tissue must play some part in the natural support of the pelvic organs, there is considerable doubt as to their surgical importance. The intimate relation between the fibrous bundles of this structure and the uterine vessels and the ureter would make suturing a dangerous procedure.

Another important plane of pelvic fascia about which there is some difference of opinion is the fascia endopelvina. This is a broad, thin, fibrous sheet arising from the pelvic floor lateral to the vagina and extending from the lower border of the pubis toward the anterior aspect of the sacrum. This layer is designated as the visceral layer of the pelvic fascia by Cunningham,[5] and is stated by him to spring "from the parietal layer immediately above the origin of the levator ani and that, as it runs toward the medial plane it encloses the pelvic viscera." Tandler states that this broad sheet of connective tissue which he says is the lowest plane of the subperitoneal connective tissue and to which he applied the name tela endopelvina, since he limits the term fascia to true muscle fascia, extends from the symphysis in a laterally convex curve to the ischial spine, from which it radiates toward the connective tissue on the anterior aspect of the sacrum. He further states that "the whole expansive structure is, accordingly, laterally convex and medially cut three times concave around the bladder, vagina, and rectum."

In a recent article I[6] described this structure and stated that a broad sheet of fascia was found to arise from the fascia covering the superior surface of the levator ani muscle. Its line of origin extended from the lateral portion of the inferior border of the body of the pubis back to a point just medial to the spine of the ischium. Its dorsal border blends by means of loose areolar tissue with the fascia covering the pelvic aspect of the sacrum. To this layer I gave the name "main sheet" of pelvic fascia. This main sheet in the dorsal half of the pelvis rises cranially 5 to 6 cm. to form the uterosacral ligaments. Ventrally, at the lateral border of the cervix and vagina it divides to surround these organs forming the prevaginal and retrovaginal layers of fascia. This description was found to agree in general with that of Tandler's tela endopelvina. I could not agree, however, with Tandler and others that this layer has its origin in the subperitoneal connective tissue. On further study it was noted that the superior levator fascia covering the cranial surface of that muscle did not do so in a complete and uninterrupted manner. At a point about 1 or 2 cm. from the origin of the muscle, it was found that the superior levator fascia left the muscle to form the fascia endopelvina (main sheet of pelvic fascia), and it was demonstrated that the latter was, therefore, composed of two layers. Therefore, the fascia endopelvina is defined as a double layer of fascia extending as a mesentery-like structure from the pelvic floor to the lateral margin of the vagina over the walls of which its two leaves spread.

In an histologic study made by me[7] it was found, in a section of the pelvic organs of a twenty-two-month-old infant, that the thin fascia endopelvina passed behind the rectum and gave no evidence of its origin from the superior levator fascia (Fig. 7, Ref. 7). This presents evidence more to substantiate Tandler, Davies and others, than my own gross dissections described above. However, Halban has stated that the fascia endopelvina is a direct continuation of the fascia endoabdominalis, that it lines the pelvic cavity and *covers the uterus, vagina, and bladder.* This point is, however, more academic than clinical.

The next point for debate is the presence and origin of a definite perivaginal fascia. I have stated that the "main sheet," fascia endopelvina, splits to surround the vagina, the lateral layer forming a definite prevaginal fascia and the medial leaf a retrovaginal fascia. This agrees with Tandler, Cunningham and many others who describe a definite dissectable layer of fascia around the vagina.

Goff[8] was one of the first to dispute this generally accepted point of view, and it is largely to him we owe our knowledge of the importance of histologic study of the pelvic connective tissue. Goff states in his conclusions that "there is a thin layer of fascia of areolar type between the anterior vaginal wall and the bladder, and a similar layer of areolar fascia between the posterior vaginal wall and the rectum. These layers, he continues, unite at the side of the vagina to form the perivaginal fascia

which is a part of the fascia endopelvina. However, he states that the areolar character of this fascia makes it impossible to dissect it as an individual layer.'' Koster agrees with Goff in this. Goff, Koster and the writer agree that no plane of fascia exists between the urethra and vagina.

In my second paper I reported an histologic study of the perivaginal connective tissue of an adult nullipara and two infants. The sections were taken through a plane between the cervix and the upper end of the urethra and after the usual celloidin technic of embedding, were stained with hematoxylin, eosin and orange G. for connective tissue differentiation. At the lateral margin, anteriorly, loose but definite connective tissue strands were found on, and fused with, the muscle of the vaginal wall. Toward the center they became very thin until they could scarcely be distinguished. In some areas definite fibroelastic bundles were seen. The blood vessels approaching the vaginal wall were surrounded by loose areolar tissue which fused with the thin layer of fascia endopelvina as it reached the lateral vaginal wall. Along the posterior wall a more definite and continuous strand extended across the vagina closely fused with the vaginal musculature and traced laterally as a layer of the fascia endopelvina.

From this study I was able to modify and to some extent clarify my former opinions. Although these perivaginal layers, continuous with the endopelvic fascia, were present as definite bands of connective tissue of varying density and were present as early as the eighth month of life; they were in the main too thin to be easily dissectable.

It is evident from the foregoing study and from the work of Goff and of Koster that definite dissectible planes of fascia do not surround the vagina. Therefore, it becomes important to determine the structure of the broad planes of tissue obtained in the dissecting room and at the operating table. Bissel[9] removed sections of the anterior vaginal wall during operations for cystocele and found in them no evidence of fascia. In this regard, Koster makes the following statement: ''In our operative material we have never been able to demonstrate any fascia in the rectovaginal or vesicovaginal septa. The only tissue to be found there, other than the mucosa is a loose, areolar connective tissue which can have no restraining or supportive value.''

In the study to be reported here, tissue was removed from the anterior and posterior fascial planes of the vagina at operation. In obtaining specimens of the prevaginal ''fascia'' the typical Rawls[10]-Neel[11] ''fascia overlapping'' operation was done. A strip was taken from the outer third of the so-called fascia. This part was chosen because my former studies had shown the fascia to be denser at this point. This tissue was mounted on gauze and labelled so as to determine the vaginal and vesical aspects, embedded with the usual celloidin technic, cut and stained the hematoxylin, eosin and orange G. for connective tissue dif-

ferentiation. To obtain the sections of retrovaginal "fascia," this layer was exposed by carefully dissecting away the vaginal mucosa according to the method of Clark.[12] A firm thin layer of glistening tissue was, as usual, exposed. Sections were taken from this, carefully labelled and

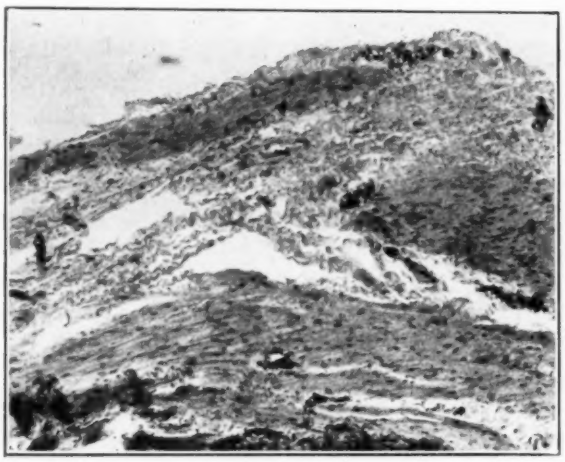

Fig. 1.—Section of tissue removed from the anterior vaginal wall during fascia overlapping operation. Most of the lower half is composed of muscle bands with strands of fascia between them. There is a broad band of fascia extending obliquely upward across the upper half of section. Note wavy lines of elastic tissue, left center. Vesicle aspect is uppermost.

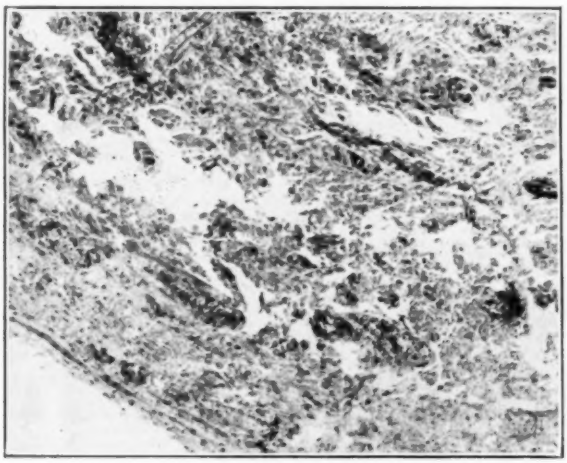

Fig. 2.—Section of dissected layer from posterior vaginal wall. In this section is seen very little muscle. Most of tissue is a compact connective tissue, with here and there strands of muscle. The rectal aspect is below.

treated with same technic as described above. With the stain used, the muscle appears a light red and the connective and fibroelastic tissues are stained a pale yellow.

The specimen (Fig. 1) removed from the anterior wall is found to be made up of the many bands of muscle, blood vessels of varying size, areolar tissue and fibro-

elastic connective tissue. These bundles appear between the muscle fibers throughout the entire section, but over the vesical aspect of this tissue at its most lateral point, there is a marked condensation of connective tissue containing many strands of fibroelastic tissue.

The specimen (Fig. 2) removed from the posterior vaginal wall, although containing some muscle fibers is made up principally of a rather compact connective tissue with strands of fibroelastic tissue interspersed. Over the rectal aspect of the tissue the density of the connective tissue is increased. In general the fascial structure of these specimens agrees with that described in my former paper.

It is apparent from this study that although definite broad firm sheets of tissue can be dissected from the vaginal walls, they are not composed of fascia alone, but of muscle, connective tissue and compact strands of fibroelastic tissue, the latter intermingling with muscle bundles but appearing as definite broad strands along the surface of the vaginal musculature. The muscle is more in evidence in sections obtained from the anterior wall. In a previous report I demonstrated that these strands of connective tissue are continuous with the fascia endopelvina, a fact also noted by Tandler and others.

For the past ten years I have used these musculofascial planes as the principal supportive factor in the surgical treatment of uterine prolapse. The results have been quite satisfactory and will be reported in a later paper.

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505 Medical Arts Building

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Ellenberg investigated the sedimentation rate in newborn infants by the Linzenmeir macromethod. The blood was drawn from the anterior fontanel. The ages varied from two to ten days. The sedimentation time in the normal newborn infant ranged from seven to twenty-three hours, with the average sedimentation speed for the entire neonatal period at fifteen hours as compared with two hours which is considered normal in adults. There is also a tendency for the sedimentation reaction to become less prolonged as the infant grows older.

W. B. Serbin.

CHORIONEPITHELIOMA WITH A LONG LATENT PERIOD*

DAVID FEINER, M.D., F.A.C.S., BROOKLYN, N. Y.

THIS case of chorionepithelioma is reported chiefly to emphasize the fact that a long insidious, latent period may intervene between the original pregnancy and the subsequent malignant tumor. Fortunately, we now possess hormone tests by means of which the diagnosis may be established in suspected cases during this dormant period, long before secondary metastatic manifestations make the condition obvious.

The simple invasion of the myometrium by trophoblastic, syncytial wandering cells, or multiform giant cells, may occur in any case of normal pregnancy. Likewise, there may occur prolonged retention of placental remnants as reported by Tritsch, who mentions cases in which placental tissue remained in utero for varying periods of from one week to six years without symptoms. Ries reported a case in which he found degenerated villi in the veins and walls of a uterus removed for fibroid eighteen years after the last pregnancy. If, weeks or months after a delivery, miscarriage, or hydatid mole, large masses of cells of fetal origin, which appear to be actively proliferating and replacing areas of the myometrium, are found, we have a potential malignancy.

A point, however, about which there appears to be but very indefinite knowledge, is how long such fetal elements may remain dormant and yet potentially active in the maternal organism after the termination of the gestation proper. In other words, how long after the last pregnancy may a tumor conceivably arise from such cells. Marchand, whose pioneer studies of chorionepithelioma date back to 1895, stated, even at that time, that we have no definite data for determining how long chorionic epithelium may remain alive in a closed vessel lumen, or a healed-over placental rest. The average interval in most of the cases reported has varied from one to twelve months. When the interim has been longer, there arises the suspicion that there has been an intervening pregnancy with early miscarriage which has been overlooked. A sufficient number of cases have been reported in which the interposing dormant period between the last demonstrable pregnancy and the development of a definite chorionepithelioma, either in the uterus or elsewhere, has been of very considerable length. This tends to establish with certainty the fact that far-reaching changes in the maternal organisms are capable of converting into malignant cells fetal elements which were encased within it in a friendly, inactive state for years, or decades, thus giving rise to a malignant tumor of the type under discussion. As

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indisputable evidence are those cases of chorionepithelioma appearing after the menopause. The most comprehensive article on the subject is by Krosing (1909) with a complete résumé of 21 cases reported up to that time, to which she added one of her own. We have collected 25 additional cases which have appeared since in the literature. Of these 46 cases, the latent period has varied from one to thirty years. A further analysis of this material reveals the following:

10 cases appeared in the third decade
11 cases appeared in the fourth decade
10 cases appeared in the fifth decade
13 cases appeared in the sixth decade

Of particular importance is the fact that 23 cases appeared after the menopause.

15 cases followed hydatid mole
14 cases followed normal full-term delivery
14 cases followed miscarriage

CASE REPORT

Patient, M. G., twenty-eight years of age, suffered the usual childhood diseases which left no residual pathology. At twelve years of age, following the death of a friend, she developed a marked fear of death. This was so pronounced that she experienced a nervous collapse several times prior to her marriage at twenty-one years of age, and about once a year after marriage. It was her custom never to be unescorted on a trip, or even a shopping tour, lest she become ill among strangers. In spite of this unusual mental complex, she was a very highly regarded teacher at school.

During December of 1930, at the age of twenty-five, two and one-half years prior to the time she was seen by us, the patient became pregnant for the first time. When she was four and one-half months gravid she spontaneously miscarried. An attending gynecologist at a local hospital performed a curettage for retained secundines. As she continued to bleed, a second curettage was performed ten days later. Examination of the curettings revealed no evidence of chorionepithelioma. Vaginal bleeding persisted and a third curettage was performed about two weeks after the second. One of the pathologists at the hospital thought these curettings were suspicious of chorionepithelioma. However, careful examination of the slides by a number of prominent pathologists throughout the city failed to reveal any evidence of malignancy. The last curettings were obtained more than three weeks after the miscarriage. Bleeding ceased soon after the third curettage, and the patient was discharged as cured.

For a period of two years thereafter she enjoyed unusually good health. She indulged in competitive sports with no evidence of fatigue. The first sign of illness made its appearance during May, 1933, about two and one-half years after her pregnancy. There had been no evidence of a subsequent conception during the interim. A scant menstrual period occurred in May, followed by some intermenstrual staining. During this period it was noted that the patient was becoming progressively paler. She began to suffer from weakness and headaches. Repeated pelvic examinations showed a small uterus of normal consistency. A complete general examination failed to reveal any cause for her anemia. Glandular and hemitinic medications were given with no effect. At the end of May the hemoglobin was 45 per cent

and the erythrocyte count 2,000,000 per c.mm. A thorough hematologic study failed to reveal any evidence of a blood dyscrasia. The anemia continued to be rapidly progressive and the patient began to vomit. This was attributed to the liver extract given by mouth, which had always caused nausea. Repeated chest examinations were negative. At this time we recalled the patient's history of a miscarriage two and one half years previously, followed by continued bleeding and repeated curettages. Mindful of the possibility of a chorionepithelioma following a long latent period, a Friedman test was done and proved to be strongly positive. Hospitalization was urged for more intensive investigation, but was refused. Because of her marked weakness and severe anemia, a blood transfusion was given at home, about the middle of June. On the following day a profuse hemorrhage occurred from a small bluish mass which had appeared on the perineum, above the anal sphincter. This growth, which was cystic and about the size of a marble, had the appearance of a thrombosed hemorrhoid.

The patient was admitted to the Israel Zion Hospital. The perineal mass, which had already become necrotic and ulcerated, was excised. It proved to be a chorion-

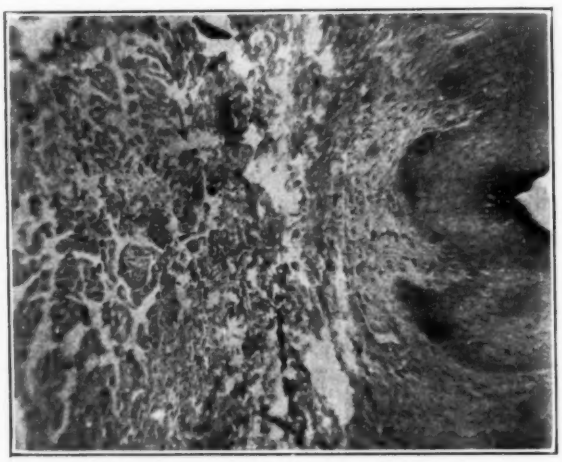

Fig. 1.—Anal wall showing submucosal syncytial cell portion of chorionepithelioma.

epithelioma. An x-ray of the chest on the following day showed the lungs to be studded with metastases. Both lung fields contained many rounded deposits, ranging in size from one to three inches in diameter. Two days after the metastatic deposits were demonstrated, the patient began to cough, and from this time on she exhibited increasing evidence of the malignancy of her condition. Painful cough with bloody expectoration, while mild at first, became very discomforting and most difficult to control. Vomiting became usual after each meal, as did also severe abdominal pain. At no time was there more than slight vaginal bleeding, or any palpable pelvic pathology. Severe frontal headaches were common and weakness was marked. The abdomen was distended and tender and the liver enlarged to as low as four fingers below the costal margin. With all these distressing symptoms her mental faculties remained acute until she passed into a coma six hours before death.

The laboratory report of the excised anal nodule is as follows:

The submucosal connective tissue, right beneath the epidermis, was the seat of a tumor mass which was necrotic to a certain extent. Islands of tumor tissue consisted of polygonal cells, similar to the Langhans' cells of the chorion. These cells were quite polymorphous and their nuclei showed considerable variations as to size

and shape. Mitoses were frequent. There were also scattered syncytial protoplasmal masses which contained a large number of nuclei, some vascular and some hyperchromatic.

The clinical value of the Aschheim-Zondek test in doubtful cases during the dormant period, cannot be too strongly emphasized. Previous to the utilization of this test, the diagnosis of chorionepithelioma was not made until we had a palpable uterine mass, positive curettings, or pulmonary or vaginal metastases. Curettage has been notoriously unsatisfactory owing to the possible location of the tumor at a distance from the endometrium. The suggestion of Vineberg to perform a vaginal hysterotomy and digitally explore the interior of the uterus has

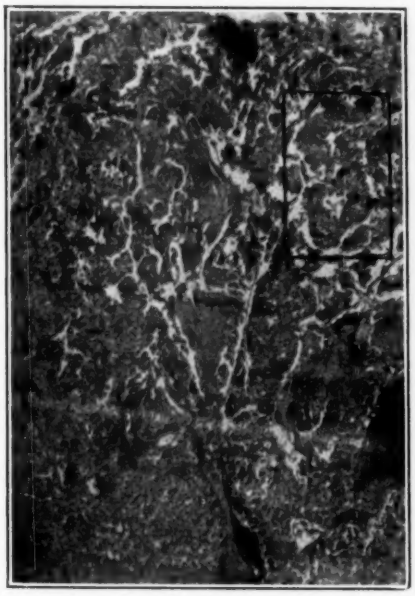

Fig. 2.

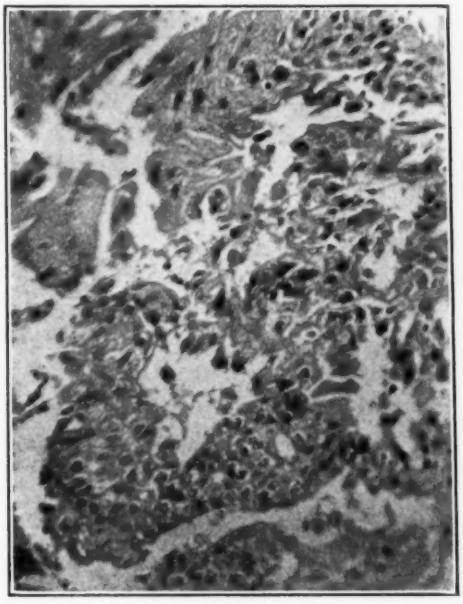

Fig. 3.

Fig. 2.—Metastatic chorionepithelioma in rectum. Note central sheets of syncytial cells surrounded by masses of Langhans' cells.

Fig. 3.—High power of inset of Fig. 2. The two cell-types of chorionepithelioma clearly shown here.

been a considerable advance. The microscopic examination of the curettings is further complicated by the fact that the chorionic epithelium is normally a proliferative and invasive tissue showing a tendency to persist and penetrate to a considerable depth into the uterine musculature. This is especially marked when the syncytial coverings proliferate for no accountable reason and form polypoid processes which invade the surrounding tissue and lodge in the uterine and even in distant veins (Schmorl).

In 1929 Fels and Rossler demonstrated that hydatid mole and chorionepithelioma excrete many times more of hormone than the normally

pregnant, and that *quantitative* estimation by the fractional method of hormone excreted is an accurate guide in differentiating hydatid mole from uterine bleeding in the course of pregnancy due to other causes. Further investigations revealed that the presence of increasing quantities of hormone two weeks after the termination of normal pregnancy, or eight weeks after a molar pregnancy, is pathognomonic of chorionepithelioma. Thus far, approximately 50 cases of chorionepithelioma have been studied by means of the Aschheim-Zondek test, proving the value of the test in the diagnosis and prognosis of hydatid mole and chorionepithelioma. Estimation of quantitative differences in evaluating a persistent Aschheim-Zondek reaction is most important, and though clinical manifestations may be absent, an amount of gonadotropic substance in the urine in excess of 20,000 mouse units per liter, indicates an early chorionepithelioma. Levinthal and Saphir report a case of early chorionepithelioma diagnosed and operated upon solely on the basis of the laboratory findings of a strongly positive Aschheim-Zondek test with quantitatively 333,000 mouse units per liter of urine, in a patient who had expelled a hydatid mole four and one-half months previously.

SUMMARY AND CONCLUSIONS

A case is reported of the occurrence in a woman aged twenty-eight years, of a vaginal tumor possessing the histologic structure of a malignant chorionepithelioma two and one-half years after the last demonstrable pregnancy.

In view of the number of well-authenticated similar cases reported in the literature, we are forced to the conclusion that, whereas in the vast majority of cases all fetal elements are destroyed by the maternal tissue within a comparatively short time after the termination of pregnancy, in exceptional instances fetal epithelia may remain dormant in the maternal host, either at the placental site or elsewhere, for months or years, then to be, by some unknown agency, stimulated to malignant proliferation. The fact that many of these cases have developed long after the menopause would effectually disprove the theory that in all such cases an intervening pregnancy has escaped detection. It is to be regretted that the Aschheim-Zondek test was not utilized earlier in the course of this case, in which event a prompt hysterectomy might have stayed the progress of the disease.

875 St. Mark's Avenue

REPORT OF A CASE OF LUTEOMA WITH REVIEW OF THE LITERATURE

SEWARD H. WILLS, M.D., F.A.C.S., AND SAMUEL A. ROMANO, B.S., M.D.,
NEW ORLEANS, LA.

(From the Departments of Gynecology of Tulane University of Louisiana and Charity Hospital)

GLYNN[1] used the term "luteoma" to describe lutein cell tumors. He reviewed the literature up to 1920, and collected fourteen ovarian tumors described as "lutein in origin"; of these nine were fully recorded, five briefly recorded. In this same article Glynn has collected ten cases reported as "ovarian hypernephromas," and in his discussion he presents evidence that these "ovarian hypernephromas" are probably of lutein cell origin.

Novak and TeLinde[2] did not consider the evidence for the lutein origin of all the fourteen cases mentioned above convincing, and objected to all five of the briefly recorded cases and specifically to two of the remaining nine. One of these reported by Schaller and Pforringer, in 1899, as an instance of carcinomatous degeneration following cystic transformation of the corpora, Novak and TeLinde point out is merely an example of multiple theca lutein cysts of the ovary associated with hydatid mole. In this case such a mole was expelled from the uterus twelve days after operation. The other case, reported by Grouzdew in 1903, was objected to because after operation the tumor recurred in the lymphatic glands and on the peritoneum as a spindle cell sarcoma.

In a review of the literature since 1920 we were able to find three cases reported as luteomas, those of Wolfe,[3] Cosacesco,[4] and McIntyre.[5]

The following is reported as an additional case:

E. F., aged twenty-six, a colored married woman admitted to the Charity Hospital April 16, 1934. Her chief complaints were pains in the left lower abdomen for six weeks, and an amenorrhea of nine months' duration. She had two children, ages five and ten, normal labors and puerperiums. No abortions or miscarriages. Nothing of importance in the family, urinary, or gastrointestinal histories. Her menses began at thirteen, interval and duration perfectly normal until 1930, when she had irregular frequent bleeding. After three months of such irregular bleeding she states that she had a "vaginal operation," following which she had no further irregularities until 1933. The exact nature of this operation is unknown, as the patient was operated upon in another hospital and the record could not be obtained. She was told at that time that she had a "small cyst on one ovary."

During March, April, May, and June of 1933 she had vaginal bleeding nearly every day, using three or four pads. Associated was a cramplike discomfort in the lower abdomen, never severe. In July, 1933, without treatment, the bleeding checked and there followed a period of amenorrhea, until her admission in April, 1934. During the six weeks preceding admission she had pulling, dragging sensations with an occasional cramplike pain in the lower left abdomen.

Examination.—Temperature 99°, pulse 82, respirations 20, blood pressure 152/84. Urine negative. Red blood cells 4,000,000 c.mm. Hemoglobin 85 per cent (Talqvist), Wassermann negative, sedimentation time three hours. General development good; slight hypertension. Secretion could be expressed from both breasts. Abdominal examination revealed no masses or tenderness. The pelvic examination revealed

moderate relaxation of the perineum and small lacerations of the cervix. The fundus was found to be normal in size and position and freely movable. The right adnexa were normal to palpation. In the left adnexal region there was an irregular, hard mass, about the size of a large lemon, freely movable and not tender.

Operation.—April 24, 1934, laparotomy. A yellowish solid tumor of the left ovary, about 7 by 4 by 3 cm. in size, was found. The tunica and serous coat seemed to be everywhere intact. No adhesions were noted about the tumor. The right ovary was small, of normal consistency, and a small developing follicle presented at the surface. Both tubes and the fundus of the uterus were normal. The parametrium and the culdesac were normal to inspection and palpation. A left salpingo-oophorectomy and an appendectomy were done.

The postoperative course was uneventful. The incision healed by primary union. The patient was discharged May 4, 1934. The discharge examination revealed secretion still present in both breasts. There was no induration or tenderness in either adnexa, the uterus was in good position and freely movable.

Follow-up.—The patient was seen again on June 18, 1934. She stated that on May 20, twenty-six days after operation, she had a normal menstrual period of four days. No dysmenorrhea. Examination at this time revealed secretion in the

Fig. 1.—Longitudinal section of ovary.

right breast, but none in the left. The pelvic examination revealed the uterus freely movable; no tenderness or masses in the adnexa. The patient has been seen each month until Nov. 8, 1934. She has been in good health and has menstruated every twenty-six or twenty-seven days, duration three to four days. No dysmenorrhea.

Pathologic Examination.—The tube showed no pathologic changes of note. The ovary measured 7 by 4 by 3 cm. Several small cysts were seen, filled with a clear yellow fluid. On section (Fig. 1), there was seen near the surface of the ovary, and extending toward the hilum, a yellow growth, of firm consistency which made up the larger part of the ovary. No cysts were seen in the yellow areas, and the capsule of the ovary seemed to be everywhere intact.

Histologically the germinal epithelial layer was not well defined, the cells appearing normal. The tunica was well defined and not invaded by tumor cells. The bulk of the organ was made up of epithelial alveoli supported by a cellular fibrous stroma. The shape and the size of the alveoli varied, and in some areas small clusters of cells were found suggesting rosette arrangement. Surrounding the tumor mass was seen a thin shell of ovarian stroma, compressed, which showed primordial follicles, an occasional old follicle cyst and several old corpora albicantes. A striking feature was that in the examination of a number of sections of the ovary only one very early developing follicle was noted; follicle development seemed to be arrested.

The component epithelial cell showed slight variation in structure. The majority of the cells were large, round, ovoid, or polygonal in form, the cell outline being distinct. The cytoplasm was abundant, finely granular in appearance, but staining freely with eosin, and in many places a vacuolated appearance was presented. The nuclei were deep staining, mostly eccentrically placed (Fig. 2).

Less frequently smaller round or ovoid cells were seen with a deeper staining granular cytoplasm, their nuclei being vesicular and more centrally placed. This type of cell was especially noted in the small clusters or nests of cells (Fig. 3).

In some of the smaller alveoli (Fig. 4), the cells showed a mosaic arrangement. These cells were pale, some presenting a vacuolated appearance, the nuclei flattened out against the cell membrane; some were crescentic, suggesting a cell heavily laden with fat. The cell outlines were very distinct. Infrequently here one finds cells with a centrally placed nucleus.

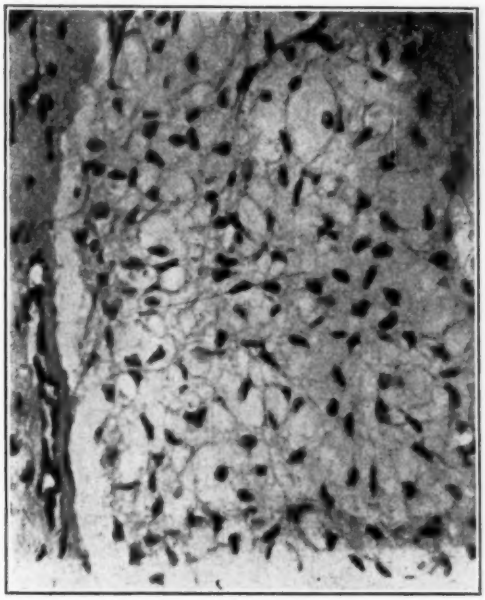

Fig. 2.

Fig. 3.

Fig. 2.—High power of an area showing the structure of the component epithelial cell.

Fig 3.—Low power of an area showing small clusters of cells.

In some areas (Fig. 5), the resemblance to a normal corpus luteum was striking, a core of cellular fibrous tissue being seen surrounded by luteinlike cells with fibrous tissue trabecula going to and from this core, dividing the cells into irregular alveoli. In these areas small vessels were seen, and the fibrous tissue trabecula seemed in places to be continuous with the adventitia of the vessels.

Intermingled with the tumor elements regressing corpora lutea were seen, and clusters of tumor cells seemed to be encroaching upon them. No mitotic figures were found. Degeneration was infrequent. The fibrous tissue stroma was of the spindle cell type and was mature. Its distribution was irregular; in some places, as in diffuse parts of the growth, only fine septa were found, in others it was found as compact zones about the alveoli.

Dr. Emil Novak was kind enough to examine a section of this tumor, and in a personal communication added a very interesting comment, which in part is as fol-

lows: "The feature which interested me most was that in some areas the constituent cells looked much more like granulosa cells than like lutein cells, and that the tendency of the cells in these regions to group themselves in small clusters and rosettes seemed quite typical of the more common granulosa cell tumor. In other areas, on the other hand, the large polyhedral, vacuolated appearance of the cells

Fig. 4.—Section showing small alveoli.

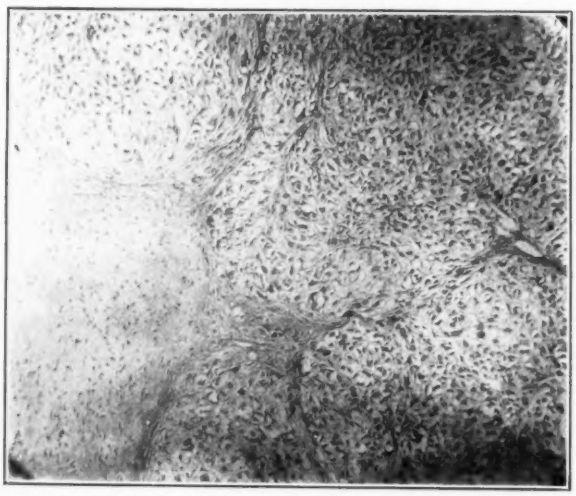

Fig. 5.—Section showing a core of cellular fibrous tissue surrounded by luteinlike cells.

and their tendency to alveolar arrangement made their resemblance to lutein cells very striking. . . . The granulosa cell appearance in parts of the section . . . lends support to the view held by many of us that the so-called luteoma is probably a granulosa-cell tumor in which the constituent cells have undergone more or less conversion into lutein cells, and that it does not arise, for example, from the transient lutein cells of the corpora lutea in the adult ovary." This possible rela-

tion of luteomas and granulosa-cell tumors is brought out in the recent study of granulosa-cell tumors by Novak and Brawner.[7] At the suggestion of Dr. Novak, special fat stains were made which showed the cells to be rich in lipoids.

SUMMARY

Since Glynn's review of the literature in 1920, we have been able to collect three cases reported as lutein cell tumors, to which we add one case.

In the case reported by S. A. Wolfe it is interesting to note that the tumor was bilateral, and that menstrual disturbances were present only two months before operation, and were of the metrorrhagic type. The left ovary was not enlarged, and though no report of its consistency was noted at operation, pathologically it was described as being of normal consistency. No note of mitotic figures was made, and the tumor was well encapsulated.

In the case reported by A. Cosacesco et al., the removal of an ovarian tumor of lutein origin was followed by normal menstruation after an amenorrhea of eight years, and during the first two and one-half years following removal of this tumor, there was a marked regression of masculine characteristics acquired during the six years preceding operation. It must be recalled that an ovarian graft was done at operation, but the authors noted that they too believed that this played no part in the clinical improvement. The symptomatology certainly suggested the possibility of an arrhenoblastoma (Meyer[8]), but there is nothing in the pathologic findings reported to suggest this.

In the case reported briefly by McIntyre as a "malignant luteinoma," both the author and Bell and Datnow expressed doubt as to the origin of the tumor.

In our case the amenorrhea of nine months, followed by normal menstruation twenty-six days after the removal of a lutein cell tumor, is very interesting, and is clinical evidence of the hormonal activity of the tumor cells. In this respect the clinical picture is similar to the case of Cosacesco et al., where after an amenorrhea of eight years, normal periods followed the removal of a lutein cell tumor. Unfortunately the tumor was fixed by formaldehyde before the exact nature of the tumor was known and a study of the hormone content of it could not be made.

The metrorrhagia of four months preceding the amenorrhea in our case is interesting also. If luteomas are luteinized granulosa-cell tumors, it serves as an explanation of this combination of symptoms.

It is unfortunate that in the cases collected since 1920 a curettage of the uterus was not done, as a study of the endometrial pattern with a lutein cell tumor should prove interesting.

In the review of cases since 1920, with the exception of the case reported by McIntyre in which the diagnosis is questionable, we find no pathologic evidence of malignancy.

We wish to express our thanks to Dr. Emil Novak for his helpful suggestions and to Dr. C. G. Collins for his excellent photographs.

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ANEMIA OF PREGNANCY

A Study of 60 Cases of the Hypochromatic Type

Francis R. Irving, M.D., F.A.C.S., Syracuse, N. Y.

AN EXAMINATION of the literature on anemia of pregnancy reveals a divergence and confusion of opinion regarding classification, cause, and treatment. This confusion results in part from a different approach to the subject by various authors. Most of the research on this subject has been done with laboratory animals, but our final opinion must be based on the response of the human subject to the various factors involved.

Although any type of anemia may be associated with pregnancy, there are two types resulting from the pregnancy itself, the pernicious and a true secondary anemia of the chlorotic or hypochromatic type. I will discuss only the latter group.

Due to the fact that pregnant women develop a varying degree of hydremia, some authorities have attempted to explain the blood changes of pregnancy on the basis of an increased blood volume, believing it to be physiologic. The results obtained by other investigators suggest that this anemia is due to the unusual demand for iron by the growing fetus and that this iron demand causes a depletion in the iron reserve of the mother.

For the past year I have made a study of the hypochromatic anemia of pregnancy. I have selected for this study sixty private patients. All patients having infections, hemorrhage, nephritis, or any apparent cause for anemia were excluded. These patients were given an adequate and balanced diet consisting of an ample supply of protein, both cooked and raw leafy vegetables, milk, and raw and cooked fruits. The red cell counts and hemoglobin determinations were taken at various times during the pregnancy and on the first day following delivery. The Sahli method was used for the estimation of hemoglobin.

I divided the patients into three groups. The first group consisted of untreated patients. The second group was given copper and iron therapy for a period of two months, following which they were given reduced iron for two months, and subsequently liver extract for two months. The third group was given copper and iron therapy throughout the prenatal period.

Chart 1 shows the red counts of forty-three untreated patients during the first trimester and the first day postpartum. It will be seen that these levels are practically the same (67 per cent). Had determinations been made on these patients a short time before delivery, they would have been lower as a result of reduction in blood volume following delivery.

Chart 2 gives the composite study of the results obtained from three different types of treatment. The group on copper and iron therapy showed an increase in their hemoglobin after two months of treatment. This group was then given reduced iron for a period of two months with the resultant decrease in the hemoglobin and red counts. They were then given liver extract with a subsequent improvement in their blood picture. The blood did not return to the levels previously obtained from the administration of copper and iron.

Chart 3 shows the average hemoglobin and red cell counts of a group of patients taking copper and iron throughout pregnancy. There is a gradual improvement in both hemoglobin levels and red cell counts before delivery and a slight drop in the

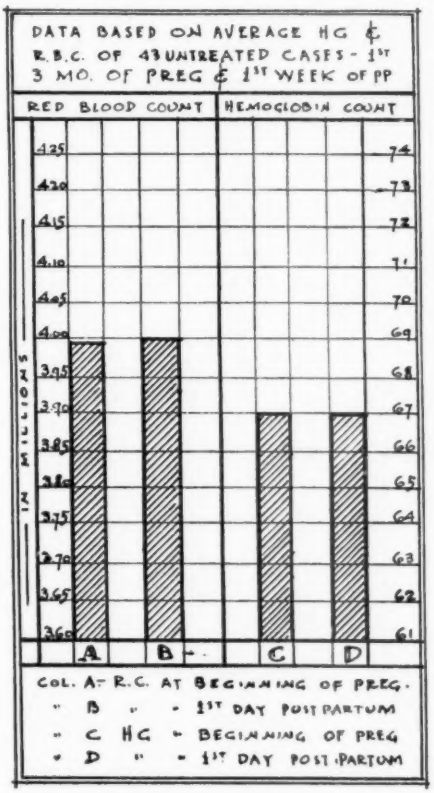

Chart 1.

red count following delivery, although the hemoglobin is at a higher level. These results are contrary to those obtained by Adamson[1] on untreated patients. My results tend to show that this anemia is not physiologic, for if this were true we would expect no improvement from treatment.

The patients studied in my series showed a hypochromatic or chlorotic type of anemia. The hemoglobin is reduced to a greater degree than the blood cells, and therefore, there is a low color index.

Clinical observations show that large amounts of liver can be effective in regeneration of blood following chronic blood loss. It should be reserved for use in the treatment of pernicious anemia, in which it

is most effective. In secondary anemia it is usually less potent and is less easy to take than copper and iron salts. Liver extract caused an improvement in the secondary anemia of pregnancy, but this improvement was less than that obtained by the copper and iron therapy (Chart 2). Steenbock[2] removed the copper and iron from liver extract by electrolysis and found the residue quite inactive. He believes that the value of liver in secondary anemia is due to the copper and iron present. Minot says of liver extract, "These extracts are not used with significant effect in secondary anemia and many patients have

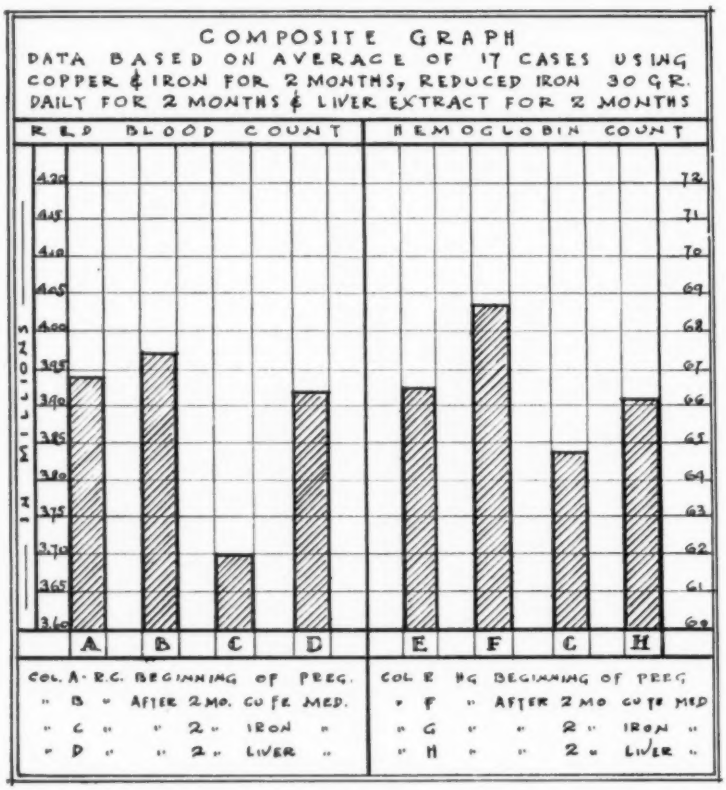

Chart 2.

wasted money and effort in buying and taking such products which cannot be expected to benefit them."

The pernicious anemia of pregnancy, in my series (macrocytic pernicious anemia of pregnancy) was not encountered. This group is characterized by Castle,[3] Whitby,[4] Mussey,[5] et al. by a high color index, megalocytosis with or without signs of blood regeneration, and is similar to Addison's pernicious anemia. These cases were first reported by Channing in 1842. According to Whitby[3] this condition is rare, especially in temperate climates. This type of pernicious anemia is controversial. Some claim it has a tendency to recur with

each pregnancy with more severity, while others believe it continues between pregnancies and is likely to become a true pernicious anemia. Abortion may be indicated in this type of anemia.

Even with an anemia in the mother, the infants are born with a normal amount of hemoglobin and a normal red cell count which rapidly diminishes during the first few weeks of life. This is probably due to the insufficient supply of iron in the milk diet. The baby derives a supply of copper and iron from the mother even when the mother's copper and iron supply is inadequate for her own needs. If

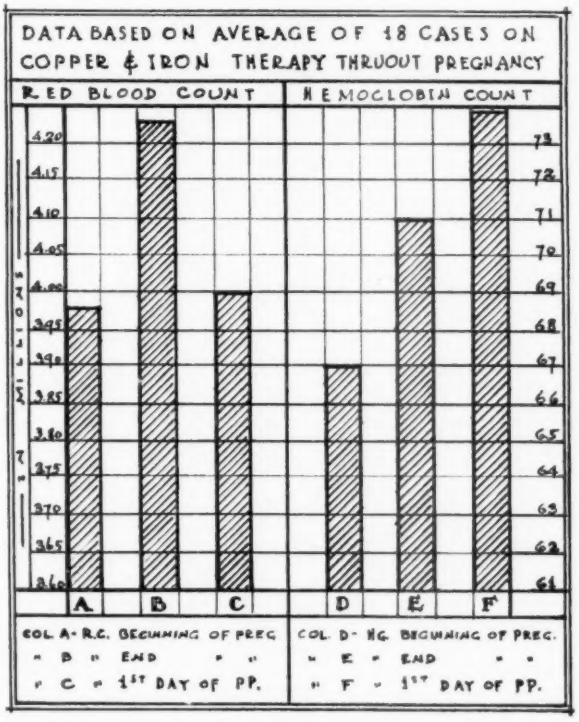

Chart 3.

sufficient copper and iron is not furnished to the mother during pregnancy, there may be an inadequate storage of these metals in the baby's tissues, resulting in the development of a secondary anemia during the first few weeks of the baby's life. Since the building materials used in the formation of the fetal blood are derived from the maternal organism, a condition analagous to chronic blood loss is present.

The Medical Research Council of England published a comprehensive investigation conducted by Dr. Helen Mackay[6] in East London from 1925 to 1930, on nutritional anemias of infancy, and their possible association with the iron supply of the mother, and its influence on

the amount stored in the fetal liver. They expressed this opinion, "It is probable that anemia in the mother predisposes to anemia in the child."

In watching the erythrocyte count and the hemoglobin levels of various patients, both with and without treatment, I have occasionally observed sudden and marked variations which were not dependent on any evident change in physical well-being. I have thought that these changes were due to sudden alterations in blood volume, and I believe that the evaluation of a therapeutic procedure in anemia of pregnancy must be gained by the study of a group of patients rather than the individual. It would seem that hydremia is a factor to be considered. I am confident that it is not the only factor operating, as my results show. This view is shared by Galloway[7] (1927), who says, "So far there has been little scientific or chemical evidence to substantiate the theory that secondary anemia is due entirely to hydremia."

The analysis and dosage of medication used in this study appears in Table I.

TABLE I. MEDICATION CHART

PREPARATION	FE.	CU.	DOSAGE
Reduced iron	95%	0.01%	0.65 gm. t.i.d.
Copper and iron (Copperin A.)	32 mg.	0.1 mg.	3 capsules per day
Liver extract (Lilly or Merrill)	0.011%	0.003%	Represents 200 to 400 gm. fresh liver daily, depending upon tolerance

This study suggests the following conclusions:

1. Secondary anemia of pregnancy is not physiologic but is caused by a constant drain on the copper and iron reserve of the mother by the demand of the growing fetus. It should be called a nutritional anemia of pregnancy, and is somewhat analagous to the nutritional anemia of infancy.

2. Patients taking copper and iron showed a gradual improvement in both red cell count and hemoglobin levels.

3. Patients taking reduced iron showed a gradual reduction in both red cells and hemoglobin.

4. Diet alone does not seem to furnish a sufficient amount of these basic metallic elements.

5. Macrocytic (pernicious) anemia of pregnancy did not occur in this group and is rare in this locality.

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713 EAST GENESEE STREET

DIATHERMY IN THE TREATMENT OF PELVIC PATHOLOGY*

NORMAN EDWIN TITUS, M.D., NEW YORK, N. Y.

(From the Department of Physical Therapy, Vanderbilt Clinic, Columbia University)

SINCE it is so well established that heat is useful in the treatment of pelvic pathology, it is not the purpose of this paper to reiterate an admitted fact. It is my desire to discuss the use of electrically created heat in different pelvic conditions that present themselves in a large clinic. The application of ordinary forms of heat to the pelvis is through douches, Sitz baths, hot water bottles, electric pads. With diathermy, however, the electrodes that touch the patient are not themselves warm, so that no conductive heat is given to the patient; the electrical energy applied is converted directly into heat. This is the essential feature which makes diathermy supreme as a method of creating heat in the pelvis, thereby inducing a physiologic hyperemia. Of course, other methods will produce a mild rise in temperature in the tissues, but electricity can produce as much temperature as desired, and the effects last for a much longer time after this treatment than with other methods.

The whole question of apparatus has never been universally decided, and it, therefore, seems fitting to express a few conclusions drawn from a very extensive clinical experience. I know many of the commercial salesmen will disagree with some of these statements, but they are only interested in selling machines and electrodes manufactured by their companies and have not the same attitude of mind as doctors whose primary interest is in obtaining satisfactory results in the treatment of their patients.

Small diathermy machines cannot produce results comparable to those obtained with large, high voltage machines. In electrical treatments of pelvic conditions, the object is to create heat in the tissues. This is done by the conversion of quantities or amperes of electrical energy. An ampere is a unit of volume of current. In order to get this electrical current evenly and smoothly distributed throughout a mass of tissue, it is necessary to have sufficient pressure to overcome varying resistances and supply ample amperage to every part. Voltage means pressure, and therefore to do efficient work, there must be sufficient voltage as well as amperage. This fact is borne out by clinical experience, and it is impractical to attempt pelvic treatments with a small machine.

*Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine, December 18, 1934.

The new method of electrically creating heat in tissues by the use of so-called radio wave machines with electrodes *not* applied to the body as diathermy electrodes is now well known. With this method the entire effect is one of high voltage with just sufficient amperage. This kind of treatment has a great future in gynecology after its limitations have been sufficiently studied The method by which these radio wave machines function is also a factor in the effects produced in treatments with ordinary diathermy machines. The advantage of the latter is that heat is produced both ways, whereas the radio waves generate the heat by a single process. In both methods, however, high voltage is a very great essential, and satisfactory results can only be obtained by large, powerful machines.

As for the electrodes containing thermometers, when one has had experience with a certain machine and these thermometer-containing electrodes, it is possible to draw approximate conclusions as to the amount of heat generated in the tissues by the thermometer reading. Diathermy electrodes are not heated by the diathermy current. They are constructed of metals that are good conductors of electricity, and the heat is only generated in the nonconducting tissues. The effect of the current on the electrodes themselves is nil, and any heating of them is due to the secondary heating of the metal by the surrounding tissues. The amount of heat generated in the tissues immediately in contact with the electrodes varies with the voltage of the machine used, and therefore, the same electrode will give different readings with different machines on the same patient. Therefore, one should not be guided by these thermometers. Experience alone teaches what dosage should be administered.

Another word of warning: Since we are attempting to establish a hypernormal circulation through the parts, we must realize our effects are upon the vasomotor regulatory system in that region. If we gradually increase the heat, the vasodilatation will be gradual, more complete, and will last much longer. If we turn on a large amount of current immediately, we can produce very marked cramps in the pelvis, adding to the discomfort of the patient, and the vasomotor system cannot react normally. Never turn on the current to full dosage, and always give the maximum available amount of time. Short treatments are almost worthless.

In general pelvic treatments with a large surfaced vaginal electrode and a belt surrounding the pelvis, the current should be sufficient to give the patient a definite sensation of warmth after the treatment has been going about ten minutes. In these cases two or three amperes of current may be used. In the treatment of gonorrhea, however, when we want to get the highest possible temperature in the tissues, in order that the temperature itself may kill the gonococci, it is necessary to

push the dosage to as high an amount as the patient can tolerate. In such treatments small machines are inefficient. When treating the cervical canal with a big machine, there is no evidence of sloughing or destruction of mucous membrane the next day, but if a low voltage machine is used, the mucous membrane will be so coagulated as to make it impossible to treat the patient again for a week or ten days.

It was mentioned above that the dispersing electrode is a belt. We have found from experience that the old technic of using a plate on the abdomen was not as effective as using a three-inch belt of soft metal completely surrounding the pelvis. This may be considered to represent the tire of a wheel. The electrode inserted corresponds to the axle and the current goes back and forth between these two electrodes like the spokes of the wheel. The tissues are most affected where the current is densest, in the region that would correspond to the hub of the wheel, the heat gradually spreading out as along the spokes.

Contraindications for the use of diathermy need not be thoroughly listed, because any gynecologist understands that heat created in a sealed-up cavity, containing pus, will only increase the pain and tend to disseminate the condition. Therefore, such things as acute salpingitis, and other ensaculated collections of pus should not be treated with diathermy. In acute gonorrheal infections, however, diathermy may be used even in pregnant women. We had one such patient at Vanderbilt Clinic who became pregnant just before acquiring gonorrhea without telling us and continued her treatments with the hope that the uterus would empty itself. This, however, did not happen. In Cumberbatch treatments, if the milliamperage is stepped up quickly, patients frequently complain of cramplike pains in the cervix, but in the few patients I have seen who had to be treated though pregnant, no abortion was produced.

In discussing electrotherapy in gynecology, it might be fitting to make mention of two forms of electrical apparatus that are used to create heat in the pelvis. In one the electrical current is used to heat the water within a sac introduced into the vagina. One apparatus has a sac of fixed form and the other has an electrode placed in a condom which is distended by injecting water into it through a special connection. In our hands these machines have not produced effects comparable with diathermy, but the latter type, in which the water can only be heated to 115°, has proved efficient for some conditions wherein diathermy is too irritating. Both these machines heat the tissues by conductive heat, the applicators themselves being hot. This method never can compete with conversive heat created in the tissues by electricity.

For the treatment of gonorrhea, the technic mentioned above has been used. The same wagon wheel action of the current is obtained, but to stress the point again, since the infection is restricted to the

urethra and cervix, I repeat, it is not the physiologic hyperemia that brings about the effects, but it is the result of the actual heat upon the gonococci. Tubal infections cannot be directly heated but have to be treated by the general hyperemia. It is worth noting that we have had a few patients with gonorrhea with definite tubal infection, who, after the infection has cleared up, became pregnant. We can, therefore, expect that the damage done to the tubes was cleared sufficiently for them to function.

The most striking observations we have been able to make from the 350 cases checked up for this report have been in those seemingly operative cases which were given a series of preoperative diathermy treatments. These patients were originally told that they needed to be put on the list for operation, but while waiting for their turn to come, they were sent to our department for pelvic diathermy. Reports on the charts show that pathology found upon operation was a far different picture than the original diagnosis, made when the patient was put on the operation list.

Let me here state regarding this series of cases that every one of them was referred to us definitely and completely diagnosed by the staff of Sloane Hospital. Our department merely treated the patients and referred them back for check-up and eventually for discharge. Conclusions drawn concerning the conditions presented were never made by the staff in the Department of Physical Therapy. Therefore, we feel that our results are worth while because they were not estimated by us but by gynecologists who made the original diagnoses. I wish to record now our thanks for this splendid cooperation.

It is to be regretted that we cannot have more specific infections to treat, but the problem of hospitalization for these patients if they became acutely sick could not be handled in a clean hospital. We, therefore, were restricted in the number that could be given ambulatory treatments, and results obtained are not comparable to my own experience in private practice, because these patients had to go on with their occupations and, frequently, had to skip treatments because of lack of funds to pay for them.

In three patients with gonorrheal arthritis who were admitted to the wards with another diagnosis, and the true etiology later discovered, our treatment of the pelvic infection while the patients were in bed showed its great effectiveness, in that the pelvic infection was entirely cleared up in less than ten treatments. One patient with suppurative arthritis of the ankle that was opened in the emergency room and admitted, showed positive smears from the wound; after four pelvic treatments, these smears failed to show gonococci. Her pelvic infection was cleared up in nine treatments and remained so over a period of four monthly examinations.

Another patient with gonorrheal arthritis of the wrist, latently diagnosed, started treatment in bed, continuing in the clinic, and though she has a very marked, severe swelling of the right wrist, she has now resumed her occupation as a concert pianist.

In all cases of gonorrhea we advise douches after the first 3 or 4 visits and also give the patients a course of ultraviolet baths. We do not stop with the first negative smears but keep the patients under continuous twice weekly treatments until three sets of negative smears have been reported. Some of the patients in our series were discharged by the staff of the Sloane Hospital because of clinical appearance after only two negative smears, but we classified these as "incomplete." All our "cleared" cases had three or more negatives.

The gonorrheal cases that we have been able to get into our department from the Sloane Clinic have numbered 30, five of which are still having treatment. We have been able to follow 12 patients until they could be declared totally cleared, which means, as stated above, that they have had three to six or more slides that were negative for gonococci, had no symptoms of any condition, no discharge, and were reported as clinically cleared up after pelvic examination by Sloane Clinic. To date there are five patients who have had only two negative slides but who were pronounced entirely cleared up and cured by the Sloane Clinic. One of these became pregnant and had a healthy child. Eight other patients have likewise been discharged by Sloane after only two sets of negative slides, but recorded as improved and, no pathology, on their charts.

There have been 280 patients treated for nongonorrheal conditions in our department, of which 40 are now under treatment. Of the 240 discharged, 107 had no final discharge note on their charts but were told by the Sloane doctors that they did not need any more diathermy. Of the remaining 173 cases, the recorded final examinations show that 61 patients did not have any pelvic pathology and 116 were so improved as to be able to be discharged by the clinic.

These nonspecific cases have represented practically every condition that can occur in the pelvis except malignancies and cysts. A great many of them were postoperative cases, where operation was necessary for some acute inflammatory condition. I shall not try to go into any list of specific conditions that can be improved by diathermy, but the patients that can be treated are practically all those with inflammation that do not require immediate surgery. There are many conditions that were so improved that subsequent operation was less radical.

The indication for diathermy in all pelvic conditions is whether improved circulation will help, but I do not believe that diathermy alone is always the complete treatment. It is sometimes necessary to electrically stimulate the uterus, as in an infantile organ, or to stimulate the entire pelvic contents to promote drainage. This is done with forms

of electricity other than high frequency, but I shall not go into these cases because the subject of this paper is the use of diathermy alone. We, in our department, do not believe that diathermy is a cure-all in any sense, but is just a means with which to attempt to restore normal circulation. This, of course, may also happen over a period of months without any treatment, but, as a member of the clinic staff stated, "diathermy seems to do in a few weeks what it takes Nature years to accomplish."

730 Fifth Avenue

TRANSVERSE CERVICAL CESAREAN SECTION*

A Critical Analysis of One Hundred and Fifty Consecutive Cases

Roy J. Heffernan, M.D., F.A.C.S., Boston, Mass.

CESAREAN section is an important contributor to maternal mortality. It has been shown by the Federal Bureau of Vital Statistics that deaths from this operation have mounted steadily during the past ten years. Moreover, as the incidence of abdominal deliveries seems to be increasing, we may expect these figures to become even more tragic during the next decade.

Two means of preventing this are suggested. First, by reducing the actual number of sections performed. Unquestionably a cesarean section is often resorted to, because it seems to be an easy solution to a difficult obstetric problem which could be solved more conservatively if proper knowledge and training in pelvic deliveries were available. But this involves that chimerical ideal of all who are interested in lowering maternal mortality, better obstetric education, pregraduate and postgraduate, and is beyond the scope of this paper.

The second method of decreasing deaths from cesarean section is by encouraging the more general adoption of the safest type of this operation. In a summary of 12 series of classical and cervical cesarean sections, collected from various parts of the country by Skeel and Jordan in 1932,† it was found that 3,468 classical sections were fatal in 192 cases (5.2 per cent) and 2,753 cases of cervical section in 70 cases (2.5 per cent).

The laparotrachelotomies show a mortality less than one-half the rate for the fundal operation. These figures become more impressive when we consider that in many instances the cervical section was chosen because the patient was in the "potentially infected" group.

The favorable aspects of the various types of laparotrachelotomy have been summarized briefly as follows: a definitely lower mortal-

*Read at a Meeting of the Boston Obstetrical Society, November 20, 1934.

†Am. J. Obst. and Gynec. 23: 172, 1932.

ity; a lower morbidity and smoother postoperative course; better healing of the uterine incision with less possibility of subsequent rupture; a minimum of intraperitoneal adhesions and by no means least important, because its lowers fetal mortality also, by lessening the number of destructive high forceps deliveries, applicability to cases after a trial labor or with ruptured membranes.

The low transverse section first described by Phaneuf in 1927, commends itself particularly because the uterine incision may always be confined to the lower segment. Before adopting the transverse incision it was sometimes found necessary in delivering a large fetal head, to extend the longitudinal incision into the body of the uterus. Also, when the operation was performed before term, the lower segment was found to be too short to permit the easy extraction of the fetus. This made it necessary either to perform an abdominal accouchement forcé or to extend the incision into the corpus uteri. This resulted in damage, often fatal, to the premature baby; or a failure to secure all the advantages that accrue from keeping the uterine incision below the isthmus. These difficulties are avoided by the transverse incision, as it may be curved with its convexity toward the symphysis, making an ample flap through which a large baby may be extracted with comparative ease. Another point in favor of the transverse incision is that less separation of the bladder from the cervix is required.

To stimulate further interest in this operation and to encourage its more general adoption, the following analysis of 150* consecutive transverse cesarean sections performed by me is presented. Six of these were ward patients, treated at St. Mary's Hospital, Dorchester. The remaining 144 were from my private and consultation practice and were attended in 14 hospitals in, or adjacent to, Boston.

INDICATIONS

The reasons for abdominal delivery are outlined in Table I. In many patients, two or more abnormalities were evident, but the most important one is recorded. As usual, cephalopelvic disproportion leads the list with 43.3 per cent. As many of the repeat operations were in this category, the actual incidence was much higher.

In the previous section group, 6 had the classical operation, 6 had both classical and cervical sections, and 26 had laparotrachelotomies. Of the latter, 18 had 2, 7 had 3, and 3 had 4 cesareans. There was a notable absence of adhesions in the last group. The bladder could, as a rule, be again separated from the lower uterine segment by finger dissection. Rarely a fibrous band required incision.

Although in many of the repeat cases at term the lower segment was found to be very thin, no weak scars were found. On the contrary, the repair had been so complete, in most instances it was not possible to determine the site of the previous incision.

*Since submitting this article for publication I have performed 14 additional transverse cervical cesarean sections, making a total of 164 cases without maternal mortality and with no additional fetal mortality.

Patients with preeclamptic toxemia and chronic nephritis were sectioned only after a thorough trial of efficient medical treatment failed to control the condition. The two eclamptics were primiparas in good condition, not in labor, with large babies.

TABLE I. INDICATIONS

	CASES	PER CENT
Cephalopelvic disproportion	65	43.3
Previous cesarean	38	25.3
Eclampsia	2	1.3
Other toxemias	19	12.6
Abruptio placentae	2	1.3
Placenta previa	11	7.3
Cardiac disease	3	2.0
Cervical stenosis	4	2.6
Myomectomy (during pregnancy)	2	1.3
Obstructing fibroid	1	0.6
Complete perineal repair	2	1.3
Old pelvic fracture (obstructed outlet)	1	0.6

Hemorrhage resulted from abruptio placentae in two cases. One had a typical uteroplacental apoplexy with extensive hemorrhagic infiltration of the myometrium which made hysterectomy necessary.

Placenta previa was judged to be complete in 5 parturients and partial in 6. Two of the complete previas occurred in multiparas, while all the remainder were primiparas. Transfusion of 500 c.c. of blood by the citrate method was necessary in 2 cases, before operation. The particular advantage of laparotrachelotomy over the classical section in placenta previa was evident in 3 cases. In one a tongue of placental tissue extended into the cervical canal. This was easily visualized and withdrawn, but this would probably not have been possible with a fundal incision. The other two patients showed large uteroplacental sinuses which were closed with x-shaped sutures. These sinuses continued to bleed freely after the fundus contracted, and clearly demonstrated why postpartum hemorrhage frequently follows placenta previa.

All three cardiac patients had severe mitral stenosis with regurgitation. One decompensated at the fifth month, but recovered and was sectioned at eight and one-half months, under local anesthesia.

The two patients requiring myomectomy during pregnancy were elderly primiparas, who were operated upon after a thorough trial of conservative treatment failed to control the symptoms of acute degeneration of the fibroid, viz, extreme pain, rise of temperature and flowing. One gravida was three and one-half and the other four months pregnant. At term both had large babies and in one the pelvic outlet was contracted.

The case of fetal distress occurred in a normal primipara of thirty-five, married five years, who was seen in consultation because the fetal heart was failing. Labor had been in progress for six hours. There was no disproportion, the position was left anterior, with the vertex dipping into the pelvic inlet, not engaged. The membranes were intact, the cervix about one-half effaced and two fingers dilated. The fetal heart was 144 on admission and had dropped during the last three hours to 112, with slight irregularity. On section, the cord was found to be tightly coiled around the baby's neck 3 times and the amniotic sac contained a large amount of meconium. Following delivery the baby did very well.

INTRAVENOUS PITUITARY EXTRACT

In the last 126 cases of the series 0.5 c.c. of pituitary extract, diluted with 4 c.c. of warm salt solution, was instilled slowly into a vein in the elbow as soon as the fetal head was delivered. This causes a prompt, firm contraction of the fundus uteri. The advantages of this are threefold: conservation of the patient's blood, spontaneous separation of the placenta, and a clearer operative field. If given *slowly*, in the above dilution, pituitary shock does not occur. Uterine tamponade was never considered necessary and no patient in the series developed postpartum hemorrhage.

DURATION OF PREGNANCY

Table II shows the length of pregnancy. All patients operated upon before the ninth lunar month were either toxemias or cardiacs.

TABLE II

Over 10 lunar months	14
9½ lunar months	119
9 lunar months	7
8½ lunar months	7
8 lunar months	2
7½ lunar months	1
	150

DURATION OF LABOR

The operation was performed after the onset of labor on 84 patients, or 56 per cent. The remaining 66, or 44 per cent, were not in labor.

Table III shows the length of labor prior to operation.

TABLE III

HOURS	CASES	PER CENT
1 to 4	4	2.6
4 to 8	5	3.3
8 to 12	11	7.3
12 to 24	45	30.0
24 to 36	11	7.3
36 to 48	4	2.6
48 to 60	3	2.0
60 to 72	1	0.6
	84	

The patient with the longest duration of labor was seen in consultation sixty-eight hours after the onset of pains. She was a primipara with a funnel pelvis and a very large baby presenting by the breech. The cervix was fully dilated and the membranes intact. The baby weighed 10 pounds 4 ounces. The mother made an uneventful recovery, and left the hospital on the thirteenth day.

MEMBRANES

Patients with intact membranes at the time of operation numbered 113, or 75.3 per cent. In 31, or 20.6 per cent, rupture had occurred and in the remaining 6, the condition of the membranes was doubtful.

One patient, a duopara aged twenty-seven, had an escape of fluid for five days. She had a justominor pelvis with a large baby, and a history of a long first labor

terminated by high forceps delivery of a stillborn baby. A third-degree laceration of the perineum resulted, which had been successfully repaired six months later. Her temperature was 99.4°. A porro operation was considered, but the uterus was not removed and the patient made a good recovery except for a rise of temperature to 102.2° on the second day.

MORBIDITY

A smooth, comfortable convalescence, with very little nausea, vomiting, or distention may usually be expected after the low transverse cesarean. Several patients in this series had one or more vaginal examinations and in four an attempt at delivery from below had been made. The last 36 patients of the series received 0.5 c.c. of pitressin every four hours for 5 doses. This seems to be helpful in stimulating peristalsis and in promoting normal bladder function.

Table IV indicates the temperatures. Fifty-nine, or 39.3 per cent had a rise of temperature over 100, persisting for twenty-four hours or longer.

TABLE IV. TEMPERATURES

DEGREES F.	CASES	PER CENT
98.6 to 100	91	60.6
100 to 101	32	21.3
101 to 102	19	12.6
102 to 103	6	4.0
103 to 104	2	1.3

Most of the elevated temperatures were of the "reaction type" and subsided to normal after three days. A definite cause for fever was demonstrable in 27 cases (Table V).

TABLE V. COMPLICATIONS OF PUERPERIUM

	CASES
Endometritis	8
Bronchitis	2
Phlebitis	5
Pneumonia (lobar)	2
Abscess of buttock (Mg.So 4 injection)	1
Parametritis	1
Wound infection	5
Pulmonary embolism	1

PORRO OPERATIONS

Two hysterectomies were performed. The first was a quadripara aged 36, nine months pregnant. Her physician had been treating a mild toxemia for 4 weeks. She suddenly was seized with severe abdominal pain and flowing. Examination revealed the characteristic symptoms of severe abruptio placentae. Labor had not started and there was a steady flow of blood from an undilated cervix. On section the myometrium was so friable and infiltrated with blood that it was necessary to do almost a complete hysterectomy to secure cervical tissue which would hold sutures. A live baby was secured and the patient recovered uneventfully. The other, a duopara, aged 34, had a large cervical fibroid, which almost filled the pelvis.

HOSPITAL STAY

Table VI lists the number of days spent in the hospital.

The patient who remained seventy-eight days was a repeat section, who entered the hospital with an unrecognized respiratory infection. After ether anesthesia,

lobar pneumonia developed, followed by bilateral femoral phlebitis. It is noteworthy that 127 patients, or 84.6 per cent left the hospital within sixteen days.

TABLE VI. HOSPITAL STAY

DAYS	PATIENTS		DAYS	PATIENTS	
11	3		17	13	
12	24		18	4	
13	33	127, or 84.6%	20	2	23, or 15.3%
14	39		24	3	
15	16		78	1	
16	12				

ANESTHESIA

Table VII shows the types of anesthesia used. Spinal anesthesia was usually employed when pulmonary complications were present. Local anesthesia (novocaine solution 0.05 per cent, with 3 drops adrenalin solution, 1-1000 to the ounce), with preliminary barbiturates, was used in the severe toxemic and cardiac patients. In these, a small amount of N_2O and O was administered while the baby was being extracted from the uterus. The gas was then removed and morphine sulphate gr. ¼ was given subcutaneously.

TABLE VII. ANESTHESIA

N_2O and ether	97
Spinal anesthesia	7
Local anesthesia	19
Avertin with ether	19
Avertin with N_2O	8
	150

Avertin, as a basal anesthesia has proved to be very satisfactory, in the latter cases of the series; when no contraindication exists it is now the anesthesia of choice. It appears to have no effect on the baby.

MORTALITY

There were no maternal deaths. One baby was stillborn and seven babies died after delivery, a neonatal mortality of 5.3 per cent.

1. Primipara, aged twenty-five, seen in consultation after an attempt at high forceps by family physician. Justominor pelvis with large baby. Fetal heart 134 and regular. After delivery, baby showed a depression from forceps over left parietal bone and died in fourteen hours from intracranial hemorrhage.

2. Primipara, aged twenty-eight. Severe preeclamptic toxemia. Local anesthesia. Premature (eight months), toxic baby. Died third day.

3. Primipara, aged twenty-nine. Complete placenta previa. Anencephalic monster.

4. Primipara, aged thirty. Severe preeclamptic toxemia. Local anesthesia. Premature (seven and one-half months) baby. Died second day.

5. Primipara, aged thirty-four. Severe preeclamptic toxemia. Local anesthesia. Premature (eight months) baby. Died second day.

6. Duopara, aged thirty-two. Repeat section at term. Seven-pound 12-ounce baby. Atelectasis pulmonum. Died third day.

7. Tertipara, aged thirty-four. Repeat section at term. Eight-pound 2-ounce baby. Cerebral hemorrhage; died second day.

8. Tertipara, aged thirty-nine. Two previous sections for cephalopelvic disproportion; first classical, other transverse cervical. Moderate preeclamptic toxemia. Two weeks before term, cessation of fetal movements with onset of labor twenty-four hours later. No fetal heart heard. Large stillborn macerated fetus. Placenta showed extensive infarction.

CONCLUSION

1. Cesarean section mortality is steadily increasing in the Registration Area of the United States.

2. The author believes that more general adoption of the cervical operation would materially decrease the number of these deaths.

3. An analytical review of 150 consecutive transverse laparotrachelotomies is presented with no maternal mortality, one stillbirth and seven neonatal deaths.

524 COMMONWEALTH AVENUE

A NEW METHOD FOR MEASURING THE BLOOD LOSS DURING THE THIRD STAGE OF LABOR

JOHN B. PASTORE, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

THE purpose of this paper is primarily to introduce a new method of accurately measuring blood loss during the third stage of labor. In a subsequent paper the results obtained with the use of the apparatus will be presented.

It is surprising to find so few procedures suggested for measuring blood loss at the time of delivery. In the usual method now in use, an attempt is made to collect the blood in a receptacle and later to measure it in a graduated glass cylinder. In 1904, Ahlfeld, who was one of the first to measure blood loss, suggested a unique method with which he was able to obtain data relating to blood loss before, during, and after the expression of the placenta.

Ahlfeld's specially constructed bed had a 22 cm. opening through the mattress into which a metal funnel was placed. A graduated cylinder on the floor served as the receptacle for the blood. A pillow was then placed over the opening and the patient's buttocks allowed to rest over this. Following delivery of the baby the pillow was replaced by a sheet with an opening over the funnel. In this way the amniotic fluid was eliminated. The blood collected in the cylinder was watched by an assistant who could warn the operator if there was an excessive amount of blood loss. Deductions for urine were also made by the assistant. As a rule, however, the patients were catheterized immediately after delivery to avoid this discrepancy. The placenta

itself and the placental blood were caught in a porcelain dish. During this procedure the assistant changed the graduated cylinder so as to obtain the loss after the expression of the placenta. The loss in each of these containers and the total were then recorded. Although this method would not be suitable for the present-day delivery, it furnished him with accurate determinations for the three phases of the third stage.

In 1919 Williams reported a series of 1,000 full-term spontaneous deliveries in which the blood loss was measured by his own method. His patients were placed on a sterile douche pan after delivery of the baby and the blood collected in the pan. After completion of the third stage the blood was measured in a graduated cylinder and recorded as the total loss.

Since then several modifications of his method have been in use. Recently the subject was covered by Calkins, who in 1929 presented a study of 853 cases with the blood loss measured by his own technic. His method is as follows: "At the first show of blood, after delivery of the child, a sterile hand basin is placed against the perineum between the vulva and the anus. The placenta and associated blood are caught in this basin. The basin is held in place until the active bleeding has been controlled. The blood in the pan is then measured in a graduate and is labeled the measured loss. In the majority of cases there is other bleeding previous to the placental stage, either from laceration or episiotomy, or subsequent to it from imperfect contraction of the uterus, injuries to the birth canal, etc. This amount is estimated, care being taken not to underestimate it. This second portion is called the estimated loss. While, theoretically, the method employed in arriving at this latter amount is subject to error, it is believed to be accurate to 25 c.c. on the average. It was selected in preference to the more accurate method of Williams because of the desire to separate the placental stage blood from other bleeding, as different factors might be involved in the two types. The sum of the measured loss and the estimated loss equals the total loss."

It would appear, therefore, that any satisfactory method should have certain prerequisites, as follows:

1. The method should not interfere with the sterile technic so essential to reduce puerperal morbidity and infection.
2. It should not interfere with operative procedures, such as operative deliveries, manual removal of placentas, repairs of perineal and cervical lacerations.
3. It should permit the accurate determination of the blood loss before, during, and after the expression of the placenta.
4. It should permit the operator to know at any one time how much blood loss the patient has sustained, so that he may be guided in the management of the third stage.
5. It should be accurate, without personal estimation of blood loss, so that data throughout the country can be compared.

The method which is now in use routinely in the Woman's Clinic of the New York Hospital has been developed to meet these requirements. The apparatus has been developed with the cooperation of the Engineering Department of the New York Hospital, and I am most grateful to Dr. H. J. Stander for placing these facilities at my disposal. The cooperation and suggestions of other members of the staff of the Woman's Clinic have been most valuable during the experimental period.

There are two principles involved in this method of measuring the blood loss. First, the blood is collected throughout the entire duration of the third stage in such a manner that the amniotic fluid and other cleansing solutions can be easily eliminated. Second, the loss is immediately registered on a manometer attached to the table and visible to the operator.

The apparatus itself consists of four different parts. Fig. 1 is a diagrammatic sketch of the table and apparatus, and in Fig. 2 the various parts of the apparatus

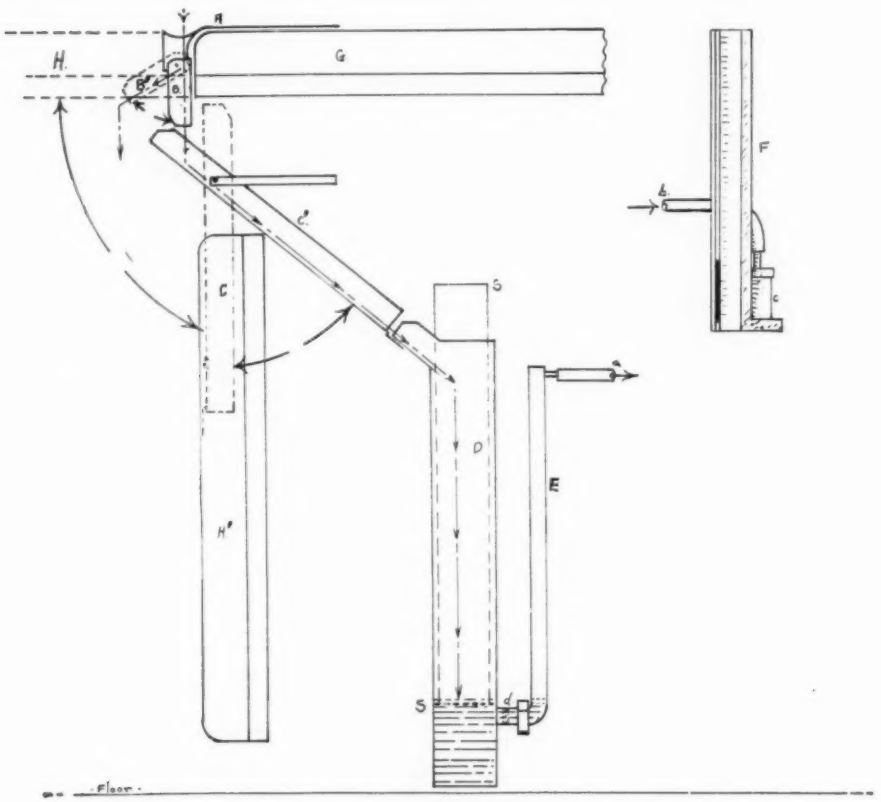

Fig. 1.—Diagrammatic sketch of apparatus and delivery table.

are pictured. The tables which are used in the Woman's Clinic are so constructed that the lower half of the table is lowered when the patient is ready for delivery. In the diagram the table is represented by the letters *G* and *H*. When the table is lowered *H* comes into position *H'*. The patient is then placed in stirrups and cleaned as per routine. A sterile Hampton pad is then placed under the buttocks. The pan *A-B* is placed under the patient and the drapes applied. This pan is of flat Monel metal and contains the adjustable trough *B*, as shown in the photograph. When the trough *B* is brought into position *B'* the amniotic fluid and the cleansing solutions are eliminated from the apparatus and drop into the waste bucket on the floor. This pan is the only part of the apparatus which is sterile and with which

the operator comes in contact. It is of such size that it can be sterilized with the instruments. The trough is left in position *B'* until after the delivery of the baby and until the flow of amniotic fluid is completed. It is then lowered to position *B* and the blood collects in the apparatus. If solutions are used to wash the perineum before repairing lacerations, the trough is left in position *B'* during the cleansing. The relative position of this trough is shown in Fig. 3.

The blood from this pan is directed through the trough *C* into the cylinder *D*. This is also of Monel metal. Because of the nature of our tables it is suspended

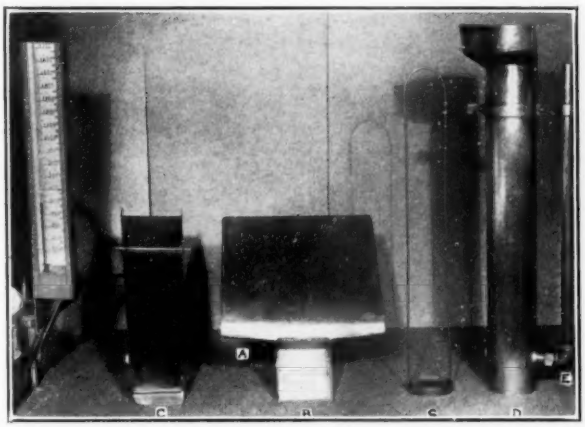

Fig. 2.—Photograph of the various parts of the apparatus.

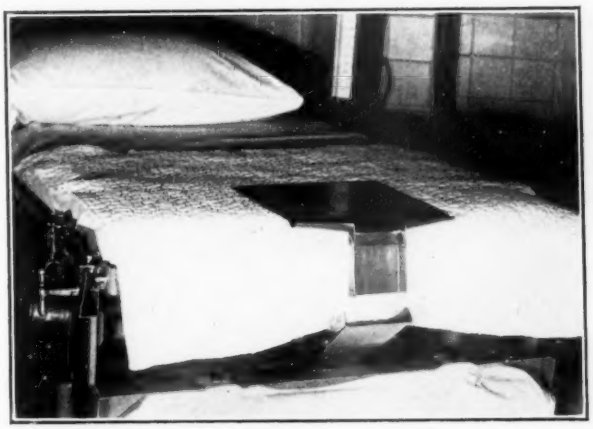

Fig. 3.—Photograph illustrating position of the trough when the blood is being collected in the apparatus.

from the table by a cross bar and rests in position *C* before the table is lowered, as shown in Fig. 4. As table *H* is lowered to position *H'*, the trough *C* is raised to position *C'*. It is easily removed, cleaned, and replaced after each delivery. With other types of delivery tables, particularly those which break into two sections, the trough *C* can remain in permanent position *C'*.

The double cylinder *D-E*, shown in Figs. 1, 2, and 4, is also attached to the table by a cross bar so that it can be easily removed and cleaned. It is constructed of brass so as to resist erosion. The two cylinders are connected at point *d*, which con-

tains a metal screen to prevent blood clots from entering cylinder *E*. In addition the circular screen *S*, shown in Fig. 2, facilitates the cleaning of the apparatus. After the cylinder is cleaned, it is filled with water to a level above *d*. The exact measurement of the water is not necessary except for purposes of checking the apparatus after delivery. We use 400 c.c. of water so that the total amount of fluid in the cylinder after delivery minus 400 c.c. should give you the amount recorded on the manometer. After the cylinder is placed in position under the table, the rubber tubing connecting it with the manometer *F* is attached at point *a*. This makes a closed system between the water level in *E* and the manometer. When the level in *D* rises the increased pressure in *E* is recorded in cubic centimeters on the manometer. The manometer, therefore, registers the increase in pressure in the cylinder *E*. This pressure is created by the increase in height of the column of blood in *D*. Since there are no mechanical parts involved in this method, the readings are not subject to error.

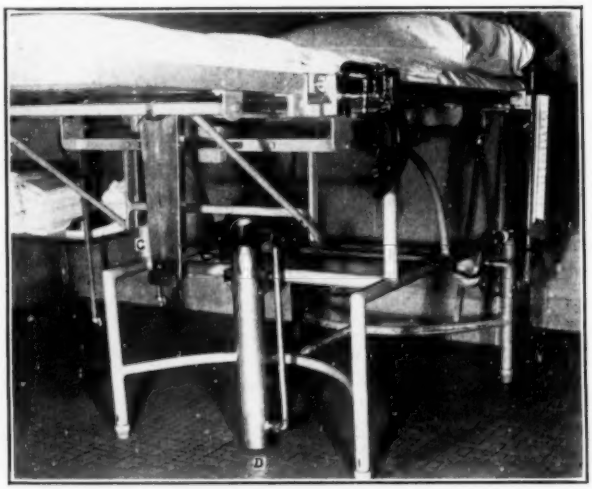

Fig. 4.—Attachment of the apparatus to the delivery table and the position of the manometer when not in use.

The manometer is attached to the head of the table on a sliding bar so that it can be lowered under the table when not in use, as shown in Fig. 4. The scale, illustrated in Fig. 5, is large enough to permit readings of 5 c.c. of blood loss. Each 100 c.c. loss equals 2 cm. on the scale. Regardless of the amount of water placed in the cylinder *D*, the reading is always zero when the rubber tubing is connected.

Because of the technicality of the above description, it seems necessary to restate that it is only necessary at the time of delivery for the operator to insert the sterile pan *A-B* under the buttocks and to adjust the trough *B* after delivery. The rest of the apparatus is cleaned and attached to the table by the orderly after each delivery so that it is always ready for the next delivery.

The apparatus offers a much more simple and accurate method of measuring the blood loss during the third stage. It measures the loss while the operator is repairing cervical or perineal lacerations. Any operative procedure may be carried out without interference. The trough in *B'* position does not interfere with forceps

delivery or version and extraction. It permits manual removal of the placenta with accurate determination of the blood loss. The placenta alone is caught in a basin and the blood allowed to flow into the apparatus.

By taking readings during the three phases of the third stage, the loss before, during, and after the expression of the placenta is determined. By knowing the exact loss at any one time, the operator is guided in the management of the third stage. Manual removal of the placenta can be carried out when it is obvious that the blood loss is becoming abnormal, as will be shown in a subsequent analytical study of the third stage.

It has proved of even greater value in cases of vaginal bleeding during the last trimester of pregnancy where vaginal examination is resorted to. The bleeding in cases of placenta previa during examination, insertion of Voorhees' bag, or Braxton Hicks version can be determined. Measurement of the amount of amniotic fluid can,

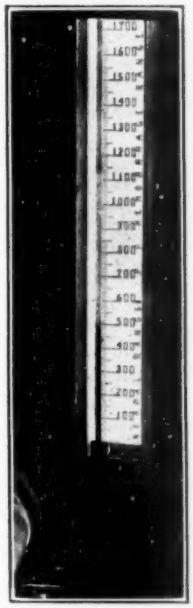

Fig. 5.—Manometer in position for use.

of course, also be made. For experimental purposes large quantities of blood can be collected, as normal saline or citrated solutions can be used to replace the water in the cylinder.

I feel quite certain that this method of determining the blood loss during the third stage of labor removes the personal equation of estimation which undoubtedly accounts for the wide variation in the blood losses reported from the various clinics. Our studies thus far on 500 consecutive deliveries have shown that estimations are inaccurate and that there is a tendency to overestimate losses below 150 c.c. and to underestimate losses above 400 c.c. The real factors responsible for excessive blood loss can be determined only when reports from the various clinics can be studied on a comparative basis.

SUMMARY

A new method of measuring the blood loss during the third stage of labor is presented. The apparatus is described in detail so that

comparative figures might be obtained from the various clinics of the country. It permits accurate determination of the blood loss throughout the entire period of the third stage. The fact that estimations of blood loss at the time of delivery are misleading cannot be overemphasized.

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AN ANALYSIS OF 1,772 ABORTIONS AND MISCARRIAGES WITH A CONSIDERATION OF TREATMENT AND PREVENTION*

Roger E. Stewart, M.D., Boston, Mass.

(From the Gynecological and Obstetrical Service of Boston City Hospital)

THIS study is based upon an analysis of 1,772 consecutive case records for the years 1929 to 1932 inclusive, at the Boston City Hospital. The term "abortion" is used in the sense given in DeLee's textbook of obstetrics, which is, extrusion of the products of conception at any time up to the twenty-sixth to twenty-eighth week of pregnancy, or the time of viability. This includes of course all cases of miscarriage in the usual understanding of the term. In each case included in the series either the pathologic report showed the presence of pregnancy, or the operator reported gross placental tissue present. The latter criterion, of course, is open to some error. Taken in connection with other facts in each case, however, such as the pelvic examination and history it is likely that the errors in diagnosis are not sufficiently great to be significant. The conventional 100.4° of temperature is used to denote a septic case, and anyone reaching or exceeding this level is so considered. Any temperature of 99° or over is considered febrile. A direct correlation has been found between the length of stay in the hospital, and the duration of the temperature. The latter is considered to be the best guide to the clinical course available, and it has been used as such. The appellation "dilatation and curettage" is used somewhat loosely to denote active intervention. Actually, probably very few of the patients required dilatation. A small number under this heading had simply manual extraction. Others had a finger curettage or removal with placental forceps. The majority had a combination of the latter with curettage.

*Read in part at the Clinical Congress of the American College of Surgeons at Boston, October 16, 1934.

The operations were done by the senior house officer. These men move up every four months, so the surgery has been done by a considerable group. The usual treatment of incomplete bleeding cases is as follows: An ampule of pituitrin and one of ergot is given on admission, and the latter is repeated for three to six doses if necessary. Hourly pulse and temperature readings with careful observation for bleeding are ordered. Markedly septic cases are put in high Fowler's position, and an ice bag was applied to the abdomen. Sedatives are given as indicated. Briskly hemorrhaging cases have the uterus emptied at once, as well as those with continued bleeding and contractions where it is obvious that the pregnancy will not continue. Bled out cases are transfused prior to operation whenever possible.

As for the actual patients: in common with other published series, it is found that the majority were married women, 91 per cent in fact. Nine per cent were single. The average number of children per case is 2.9. There was a history of previous abortion in 650 cases, and 256 cases admitted mechanical interference prior to admission. Fifty-four attempted medical induction. The average duration of pregnancy was 2.9 months. Of the 1,772 cases, 313 or 18 per cent were septic on admission, 1,481 were operated upon. The gross mortality for the series is 1.7 per cent. In other series published in recent years, the mortality runs from 0.88 per cent (Watkins) to 9 per cent (Witherspoon) the latter for operated cases only. Taussig's very large series in this country had a 2.1 per cent mortality.

There is one type of case which is of interest. It has been noted by E. B. Pearce, writing in the *Journal of Obstetrics and Gynecology of the British Empire*. This is the patient whose temperature drops suddenly, within a day or two from a high level to normal and remains normal. This type of reaction resembles very much the crisis of pneumonia. It has no apparent relation to either dilatation and curettage or spontaneous abortion in the present series. There were 124 such cases.

Unfortunately it has been found impossible to compare directly the group of cases having dilatation and curettage with those not operated upon, for the following reasons: First, the dilatation and curettage had a mortality rate of 0.9 per cent while the nondilatation and curettage had 6.2 per cent mortality. Second: 16 per cent of the dilatation and curettage group were septic on admission, while 26 per cent of the nondilatation and curettage were septic on admission. From these two facts, it is apparent that the sicker patients were treated conservatively. There is thus a definite division, clinically, within the group of septic cases.

One valid comparison can be made, however, to show the effect of surgical intervention upon patients with a septic temperature. If the

group receiving dilatation and curettage is divided into septic and nonseptic on admission, and compared for duration of temperature, it is found that those who were septic had an average of four days of temperature, while those who were not septic had 3.3 days of temperature.

If, as so many authors claim, with considerable heat and fervor, it is always dangerous and unsurgical to invade the septic endometrium, we would not expect to find, as we do here, that both operative and nonoperative septic cases became afebrile in so nearly the same short period of time. It would seem rather, that in properly selected cases, a high temperature, denoting sepsis, is not invariably a contraindication to prompt and judicious emptying of the uterus.

The sociologic aspect of these cases though not susceptible to statistical treatment is, nevertheless, interesting. It is in the large group of induced abortions that hope lies of reducing the numbers of these cases. It is a striking fact that over three hundred of these mothers admitted attempts to induce abortions on themselves. Obviously a great many more must have done so, but were unwilling to admit the fact. There is no need to dwell on the grave social consequences resulting from the loss of a mother to a home in those cases having a fatal outcome, or on the after-effects of complicated septic cases. These are self-evident. A word may be said, however, on the cost of caring for these cases. We do not know how many of the whole series of 1,772 cases were actually induced, and therefore potentially preventable. The total expense is worth considering, however. The average cost of caring for a ward patient during the year 1930 was $5.64 per day, according to the sixty-seventh annual report of the hospital. These 1,772 patients stayed a total of 13,746 days, making a total cost of $77,527.44. A not inconsiderable sum should be added to this to cover the cost of operation in the 1,481 patients so treated. There is no way of arriving at this figure since the services of the operator and anesthetist, being house officers, are free except for board and room furnished by the hospital.

Until recently there has been no means of getting at the seat of the trouble by preventing the occurrence of any considerable number of the self-induced group. Knowledge is at hand, however, and awaits only the organization of the large maternity centers of the country, to bring about a great reduction in the incidence of induced abortion. Specifically, it is the practical application of the Ogino-Knaus law of alternating sterility and fertility in the menstrual cycle.

That there is a public demand for information in regard to birth spacing and limitation is shown by the survey conducted under the auspices of the Johns Hopkins School of Public Health, by Pearl, and reported in *Human Biology* for May, 1934.

SUMMARY AND CONCLUSIONS

1. There have been 1,772 consecutive case records of abortions and miscarriages on a large metropolitan service studied for the years 1929 to 1932 inclusive.

2. The total cost of these patients to the hospital was considerably in excess of $77,527.44.

3. Ninety-one per cent were married women.

4. The mortality was 1.7 per cent.

5. There is little if any difference in duration of morbidity between the septic and nonseptic patients who were operated upon.

6. Three hundred and ten individuals admitted attempts at induction.

7. Evidence has been presented from the literature to show that means are at hand to regulate many of these unwanted pregnancies by proper organization and instruction at the large maternity centers of the country.

8. The method under consideration does not violate any religious principles or esthetic considerations.

9. The technical accuracy of the Ogino-Knaus method has been established; its social efficacy can be determined only by an adequate trial.

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201 Bay State Road

Staehler, F.: The Symptom-Free Time in Uterine Carcinoma, Arch. f. Gynäk. **153:** 561, 1933.

In a series of 200 carcinomas of the uterus, the author found that the average period without symptoms was 2.7 months. It was 4.75 months in seven patients in whom the uterine carcinoma was accidentally found. In twenty-five (1 out of 8) the carcinoma was inoperable even though the patient sought advice and treatment as early as possible, since the carcinoma had been present but latent for 4.5 months. There is apparently no relationship between the age of the patient and the duration of the latent period.

Ralph A. Reis.

FETAL CEPHALOMETRY IN UTERO AND THE DETERMINATION OF FETAL MATURITY

HERBERT THOMS, M.D., NEW HAVEN, CONN.

(From the Department of Obstetrics and Gynecology, Yale University School of Medicine)

IN 1930[1, 2] I published two papers relating to the use of roentgenometry in determining the occipitofrontal diameter of the fetal head in utero. At that time I pointed out that information thus obtained served as an index to fetal maturity and also as an index of the probable biparietal diameter. Since that time the usefulness of fetal cephalometry in utero for determining fetal maturity has been emphasized by other writers, notably Jarcho[3] and Clifford.[4]

The present communication deals with further experience with the method and emphasizes again the clinical value of the procedure. Our method is an adaptation of the grid method of roentgen pelvimetry, and as I pointed out in my first communications it is accurate for clinical purposes.

To quote.—"In this method, the plane in which any diameter lies must be identified and its distance above the sensitive plate measured, in order that the amount of divergence of the roentgen rays may be corrected. In the case of the occipitofrontal diameter, the forehead and occiput must be palpated through the abdominal wall, and their respective distances from the sensitive plate measured. It will be remembered by those familiar with obstetric palpation that the identification of these two portions of the fetal head in the latter weeks of pregnancy is readily accomplished in the majority of cases. The exposure is made with the tube or target at a thirty-six-inch distance, centering as nearly as possible over the parietal region of the fetal head. Following the exposure, the patient is removed from the table, the target and exposed plate remaining in situ. A lead grid with perforations exactly 1 cm. apart is now introduced in the plane previously occupied by the occipitofrontal diameter of the fetal heal, and a flash exposure is made on the previously exposed plate. Upon development, not only will the outline of the fetal skull be seen, but also a series of dots representing the centimeter distance. Calculation of the occipitofrontal diameter is readily accomplished by calipers.

"It is obvious for the sake of accuracy that the fetal head should be movable at the superior strait. In other words, if the head is deeply and fixedly engaged in either the right or left oblique diameters of the superior strait, the shadow projected on the sensitive plate will be somewhat distorted. Experience has shown, however, that in practically all cases where a knowledge of fetal maturity is desired, no such deep engagement is present, and the fetal forehead and occiput are readily palpable through the abdominal wall.

"In order to get some idea of the amount of error which might be expected through the use of abdominal palpation to establish the plane in which the occipito-

frontal diameter lies, we conducted a series of shadowgraph experiments with a full-term infant skull, a screen, and a reflected light.

"It was found that the fetal skull could be rotated in either direction 36 degrees before the shadow of the occipitofrontal diameter was shortened a millimeter. Moving the skull forward, still maintaining its parallel position with the screen to a 13 cm. distance, reduced the shadow two millimeters in the occipitofrontal diameter, while moving the skull to 17 cm. distance increased this shadow two millimeters." We feel therefore, that the method is accurate within two to three millimeters and our results seem to support this contention.

At the time of my first communication on the subject of fetal maturity, in order to establish a working base, a statistical study was made of a relatively large number of children to determine the relationship of occipitofrontal diameter to fetal length and body weight. In a review of 446 newborn infants, 369 measured 45 cm. or over. Eighty-seven per cent of those cases which presented an occipitofrontal diameter of 11 cm. or more showed an accompanying crown heel distance of 50 to 55 cm.; 90 per cent of those cases presenting an occipitofrontal diameter of 10.5 or over showed a crown heel distance of 45 to 50 cm.; 73 per cent of those cases presenting an occipitofrontal diameter of 9.5 to 10.5 cm. showed a crown heel distance of 40 to 45 cm.; and 100 per cent of the cases showing an occipitofrontal diameter of 7.5 to 9.5 cm. showed a crown heel length of 35 to 40 cm. It would appear from these studies that in a given instance, an occipitofrontal diameter of over 10.5 cm. would be evidence of an accompanying crown heel length of 45 cm. or more.

In the relationship of the occipitofrontal diameter to the body weight 453 cases, all 3,000 gm. or under, were reviewed with the following results:

RELATION OF BODY WEIGHT TO OCCIPITOFRONTAL DIAMETER

	Total cases reviewed: 453
Weight 2,500 to 3,000 gm.	327 cases, of which 264, or 80.9 per cent, had occip. frontal diameter 11 cm. or more.
Weight 2,000 to 2,500 gm.	81 cases, of which 69, or 85.2 per cent, had occip. frontal diameter 9 to 10 cm.
Weight 1,500 to 2,000 gm.	39 cases, of which 27, or 69.2 per cent, had occip. frontal diameter 9 to 10 cm.
Weight 1,200 to 1,500 gm.	6 cases, of which 4, or 66.7 per cent, had occip. frontal diameter 8 to 9 cm.

It would appear from this table that in the instances where the occipitofrontal diameter is over 10.5 cm. an accompanying body weight of 2,500 gm. or over may be expected.

Table I represents the findings in the last 25 cases in which we have used roentgen cephalometry as a means of determining fetal matur-

ity. The maternal indications for the termination of pregnancy have included tuberculosis, pyelitis, toxemia, pernicious anemia, disproportion, and heart disease.

TABLE I

CASE	OCCIP. FRONTAL DIAMETER IN UTERO	TYPE OF BIRTH	OCCIP. FRONTAL DIAMETER AT BIRTH	CROWN HEEL DISTANCE AT BIRTH	WEIGHT AT BIRTH	HISTORY NO.
	cm.		cm.		gm.	
1	11.5	Cesarean section	11.7	51.0	3545	88010
2	10.5	Labor induction	11.0	48.0	2355	88699
3	10.3	Labor induction	10.2	48.0	2545	88855
4	11.5	Normal spontaneous	11.5	---	2920	84914
5	11.5	Cesarean section	11.6	---	3400	60826
6	10.8	Normal spontaneous	11.0	48.0	3080	51121
7	13.0	Cesarean section	12.75	---	----	(p.p. Dr. C.)
8	12.75	Cesarean section	12.5	---	4022	(p.p. Dr. C.)
9	11.5	Cesarean section	12.0	50.0	2740	89232
10	11.75	Normal spontaneous	12.0	50.5	3025	57839
11	10.5	Normal spontaneous (see text)	11.5	49.0	3360	A29086
12	11.3	Cesarean section	11.4	50.0	3085	A40414
13	10.4	Cesarean section	10.5	45.0	2055	A15343
14	10.4	Cesarean section	10.6	47.0	2550	54843
15	10.0	Labor induction	10.2	44.5	2240	A44959
16	11.25	Normal spontaneous	11.25	49.0	3045	-----
17	11.0	Normal spontaneous	11.5	51.3	3945	A29986
18	11.25	Normal spontaneous	11.75	51.0	4110	A18383
19	11.0	Normal spontaneous	11.25	48.0	2890	A29354
20	11.0	Normal spontaneous (excessive molding)	12.0	47.5	3070	4556
21	9.25	Labor induction	9.75	---	1800	44798
22	12.0	Normal spontaneous	12.0	51.0	3455	A16700
23	10.3	Normal spontaneous	10.5	47.5	2960	-----
24	11.25	Normal spontaneous	11.25	50.0	3125	A36803
25	11.25	Normal spontaneous	11.25	48.5	3145	64337

A survey of the above table offers interesting data for discussion. Those cases delivered by cesarean section, and therefore not subject to molding, show but little discrepancy between the intrauterine and postpartum measurements. In seven of the eight cases the difference was 2.5 mm. or less. There is no question in my mind, that molding which is incident to birth by the natural passages, often does affect the length of the occipitofrontal diameter. In most cases, however, this effect is not as great as usually supposed. When excessive molding has taken place as in Case 10, marked discrepancy may be expected.

I wish to call attention to Case 11 as it emphasizes another point to which I have referred. The cephalogram in this case was made when the patient had experienced four hours of active labor and the occiput was definitely in the right occipitoposterior position and deeply engaged. This condition is easily discernible in the film, and a marked discrepancy in the intrauterine and postpartum measurements was expected.

The last ten cases of this series are those taken in connection with a study of fetal head molding and the postpartum measurement was made by means of roentgenometry exactly one hour after the birth. This method was used in order to eliminate the thickness of the scalp and the results are very accurate. I am confident that the uniformly slight increase in the postpartum measurement of the occipitofrontal diameter in these cases is the result of molding incident to birth.

To summarize this series, excluding Case 20 and Case 11, we find that there was no difference in the antepartum and postpartum measurement in four cases; a difference of 1 mm. in 4 cases; a difference of 2.00-2.5 mm. in 10 cases; a difference of 5 mm. in 5 cases.

I am convinced that the best index to fetal age is that of fetal length or crown heel distance. Reed[5] has emphasized the fact that the fetus puts on weight in the uterus as easily and as variably as after birth, and that it appears that weight is a sign of present nutrition while length is an indication of past assimilation. Bossi[6] regards the weight of the fetus as of no importance in the diagnosis of postmaturity but places great reliance on the fetal length in association with the development of the bones. It appears, therefore, that in discussing fetal maturity, we should become more familiar with the fetal length relationship rather than the traditional fetal weight relationship. The proof of this is exemplified in Case 12 where the infant delivered by cesarean section had a crown heel distance of 45 cm. and a body weight of only 2,045 gm.

To recapitulate: (1) The estimation of fetal maturity in utero by means of determining the length of the fetal occipitofrontal diameter is a most useful clinical procedure. (2) The grid method which in this clinic and elsewhere has given satisfactory results has an advantage in that it is unusually rapid and simple to carry out. (3) The best estimate of fetal maturity is found in its relationship to fetal length or crown heel distance. Obstetricians should, therefore, familiarize themselves with this relationship.

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TUBERCULOSIS AND PREGNANCY

D. S. Brachman, M.D., D.P.H., Detroit, Mich.

FOR twenty centuries, since the time of Hippocrates, it has been claimed that tuberculosis often improves with pregnancy. There were periods when marriage with subsequent pregnancy was actually recommended for tuberculous girls. Such views were held by Sydenham, Montgomery, Clark, Warren and many others. As recently as 1918 Sabourin recommended marriage for tuberculous girls because of a resultant "degree of immunity."

Ingraham[1] believes any actual improvement that takes place may be due to enforced rest necessitated by pregnancy. He feels that such improvement is likely to be only temporary and that "after the fifth or sixth month, rapid advancement of the disease usually occurs." In 1932 Fishberg[2] wrote, "it appears that many women with active tuberculous disease feel much better, the symptoms of the disease abating to some extent during pregnancy. Perhaps an explanation may be found in the circulatory changes occurring during pregnancy. It is well known that during that period the mucous membranes of the respiratory tract are congested, and this may retard the progress of the tuberculous process for the time being, as is seen to be the result of pulmonary congestion in cases of mitral stenosis."

On the other hand Ferguson[3] states that "pregnancy at any stage, and especially when allowed to go to full term, has no ultimate or real beneficial effect on tuberculous disease." Some writers feel it is dangerous, at any stage of the disease, for a tuberculous patient to become pregnant, others going so far as to recommend emptying of the uterus in all such cases. Several authorities are of the opinion that pregnancy should be avoided by the tuberculous woman until a "cure" has been established for two or three years. Many others hold that pregnancy in the tuberculous patient has a marked deleterious effect on the disease, their opinions varying only in the degree of danger.

Hanau feels that the disease may be aggravated by aspiration of tubercle germs from upper to lower parts of the lungs following descent of the diaphragm after labor. Others have thought that anemia following loss of blood in normal labor has resulted in further disease activity, and quite a few writers blame the reactivity on the shock and strain that might occur during delivery of the child.

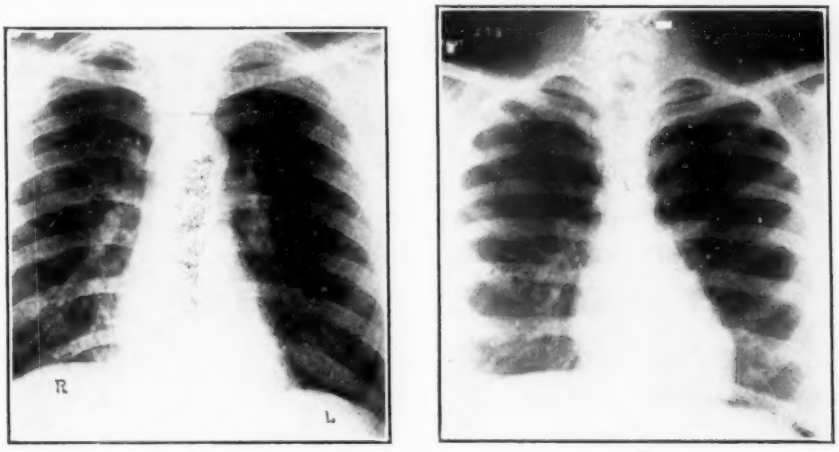
Forssner[4] in an extensive study contradicts a harmful effect on the disease by pregnancy, at least when the disease is early. Adair and Whitacre[5] give detailed figures pointing to the harmful effect, when the disease is in the second and third stages, being so slight that it may be due simply to the result of chance. They feel that harmful influence in advanced cases of tuberculosis cannot be denied. Very interesting is the conclusion of Jennings and Mariette[6] in studying 470 cases, who say "the evidence is striking that the phenomena are independent of one another." It is known that a tuberculous woman very rarely dies with a fetus in utero.

It is apparent from the mass of contradictory material available that a great deal more work will be required to unfathom these com-

plexities. This paper is intended merely to suggest a possible explanation for a few of the observations on the subject. The case given here for obvious reasons is not conclusive in any way, but it is hoped will result in discussion of the points involved.

Previously the recognized treatment for pulmonary tuberculosis was purely medical and consisted chiefly of bed rest, fresh air and sunlight, and proper food. Now, however, in modern institutions approximately 80 per cent of the patients receive some form of collapse therapy, permitting physiologic rest of the diseased area. The surgical procedures used are chiefly phrenic nerve operation, pneumothorax and thoracoplasty or a combination of these.

Phrenic nerve operation results in the paralysis of the diaphragm on the affected side, followed by as much as one-fourth to one-third limitation of lung expansion. There are two forms of this operation



A. B.

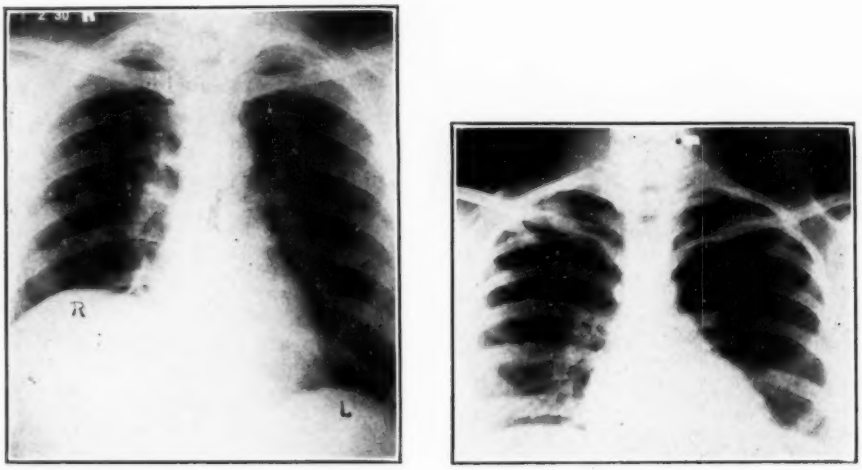
Fig. 1.—A, Showing tuberculosis in the middle of the right lung, with a cavity. Note the level of the leaves of the diaphragm, (*R*) right (*L*) left. B, The same patient approximately one month later, showing closure of the cavity, following a phrenic nerve operation. Note the elevation of the paralyzed diaphragm (*R*) on the diseased side.

(a) crushing of the phrenic nerve, giving a temporary paralysis and (b) phrenicectomy, resulting in permanent paralysis. Phrenic nerve operation is first choice in early disease in a basal lesion or when there is a small cavity. It is also used in selected more advanced cases where pneumothorax is impossible because of pleural adhesions, the chief drawback to success in suitable pneumothorax patients. A phrenicectomy is advisable, too, when allowing a lung to expand after pneumothorax.

Fig. 1, A shows pulmonary tuberculosis in the middle of the right lung, with a cavity and B the position of the diaphragm following a phrenic nerve operation with resultant closing of the cavity. This case is shown for comparative purposes.

Fig. 2, A shows the x-ray of a young woman, age twenty-two, two months pregnant. There is an area of tuberculous infiltration in the right second interspace; B shows the same patient just one week before the normal termination of pregnancy, with the tuberculous lesion healed. It is my contention that this healing could easily be the result of what might be called a physiologic bilateral elevation of the diaphragm, following the pushing upward of the abdominal contents in advancing pregnancy, simulating a phrenic crushing. An x-ray photograph of this patient six months after delivery showed no return of the disease.

Thus Fig. 2 may explain the reason for what has frequently been previously observed; namely, that some tuberculous women show improvement of the disease during pregnancy. It could also explain



A. B.

Fig. 2.—A, X-ray of a young woman, aged twenty-two, two months pregnant, showing early pulmonary tuberculosis at second right interspace. B, The same patient one week before normal labor, showing the tuberculous lesion healed. The elevation of the diaphragm here is due to pressure upward of the increased abdominal contents.

another oft discussed point, that is, the danger in the puerperium in these patients. The degree of diaphragm elevation, and the early lesion involved in Fig. 2, resulted in complete healing before the leaves of the diaphragm dropped to the normal position following delivery of the child. Were the disease still unhealed, however, one can appreciate that the sudden return of full lung expansion may result in further activity of the lesion, which, if left untreated, might go on to fatal termination.

CONCLUSIONS

Advancing pregnancy results in elevation of the diaphragm similar to that following a phrenic nerve crushing.

Though it is recognized that a single case proves very little, and appreciating that it cannot be accepted as conclusive even in the patient involved, nevertheless it is presented to stimulate discussion on the points mentioned.

If the theory is correct it definitely explains an observation made over centuries but attributed to other reasons, that is, the frequent improvement especially of early cases during pregnancy.

The rapid increase of the disease in tuberculous women immediately following labor may be explained by the sudden removal of the beneficial effect due to elevation of the diaphragm.

It is suggested that pregnancy in tuberculous women is a matter for consultation of the obstetrician with the chest specialist as to the proper procedure during and after the completion of the pregnancy. Proper collapse therapy just previous to delivery will undoubtedly improve the outlook in what might otherwise become a more serious condition.

Since it is known that up to 1 per cent of apparently healthy young adults may have active tuberculosis,[7] it is strongly advisable that all pregnant women, particularly primiparae, have an x-ray of their chest at least in the latter part of pregnancy, *irrespective of the presence or absence of symptoms or abnormal physical signs.* In this way previously unsuspected tuberculosis may be found and proper collapse treatment instigated before severe damage results.

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8921 Hamilton Avenue

Ryerson, and Sanes: The Age of Pregnancy, Arch. Path. **17:** 648, 1934.

In a study of placental tissue based upon the maturation of red blood cells in the fetus, with their development from nucleated to nonnucleated forms, the authors state that they are able to determine the age of a pregnancy. A differential enumeration of these elements in the chorionic capillaries is made and the results may be expressed in quantitative terms. The procedure consists in the examination of material obtained from paraffin sections and stained with hematoxylin and eosin. One hundred consecutive specimens of placental tissue were examined. This material was obtained following full-term delivery, curettage, abortion, or operation for ectopic pregnancy. Appropriate clinical histories accompanied all specimens. The proportions of nucleated to nonnucleated red blood cells were calculated.

Of seventy placental fragments suitable for study, it was found that replacement of nucleated by nonnucleated forms took place rapidly and almost completely during the second and third months. Therefore, if all the chorionic corpuscles are nucleated, the pregnancy is probably not older than two months. If more than 1 per cent are nucleated, the age is less than three months. If fewer than 1 per cent of the red cells are immature, pregnancy has passed beyond three months. This method, the authors claim, may be of medicolegal value. W. B. Serbin.

TUBAL ENDOMETRIOSIS SIMULATING ECTOPIC PREGNANCY*

J. Irving Kushner, M.A., M.D., New York, N. Y.

(From the Department of Pathology and Medical Research, The Bronx Hospital)

WHILE the frequency of endometriosis in tubal pregnancy is admitted, yet the literature reports only four such instances. Seitz[1] reports a case of tubal menstruation and formation of an acute hematosalpinx mistaken for a ruptured tubal pregnancy. Lee[2] reports a case of a ruptured endometrial cyst simulating intraperitoneal rupture of an ectopic pregnancy; and Sampson[3] cites two patients with postsalpingectomy endometriosis operated upon for tubal pregnancy. In both cases an endometriosis of both uterine cornu without evidence of decidual reaction were found.

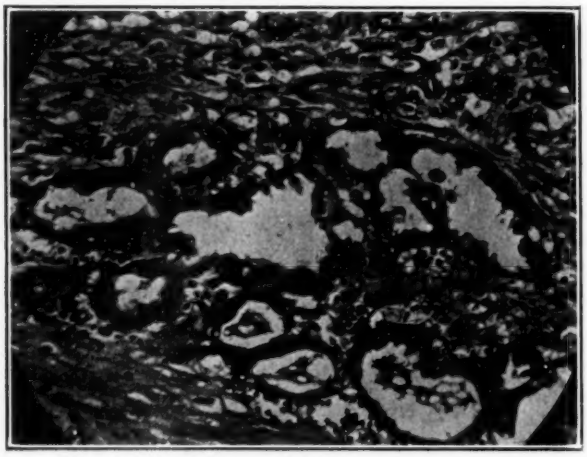

Fig. 1.—Wall of tube. Hyperplasia of wall. Uterine-like endometrial stroma, with some congestion.

The paucity of the literature on this condition led to the report of the following case:

B. G. (No. 39992), white female, aged thirty-five, admitted to the hospital because of pelvic pain and vaginal bleeding. Menses had begun at age of twelve, were of twenty-eight-day type, regular, with a four-day flow. Patient had missed her last period and almost immediately began to experience vague pelvic pain, weakness, and five days later slight vaginal bleeding.

On examination, because of tenderness in left lower quadrant, with slight enlargement of the uterus and a fixed tender mass in the left culdesac, a diagnosis of ectopic gestation was made and immediate laparotomy performed.

At operation the entire left adnexal region was found to be the seat of a mass intimately matted together about the size of an orange. There was no free blood found in the pelvic cavity. A left salpingo-oophorectomy was performed.

*Read at a meeting of the North Bronx Medical Society, November 1, 1934.

The complete pathologic report is as follows: Specimen consisted of an irregular mass 6 by 5 cm., composed of a tube and ovary intimately connected. The ovary was whitish in color, fibrotic, and contained a large irregular corpus luteum cyst. Tube was distorted, apparently the seat of a large rupture, and lumen contained some blood clots. Microscopic section of tube showed the lining hypertrophic and congested. It had the appearance of uterine endometrial stroma. There was no evidence of decidual reaction. Diagnosis: "Hyperplastic endometriosis, tubal."

I wish to express my appreciation to Dr. Joseph Felsen, Director of Laboratory and Medical Research at The Bronx Hospital for his helpful suggestions in the preparation of this report.

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169TH STREET AT FULTON AVENUE

A CASE OF TUBERCULOUS INFECTION OF THE BARTHOLINIAN GLAND

ANTHONY BASSLER, M.D., NEW YORK, N. Y.

IN A SEARCH of the literature I could find no instance of tuberculous infection of the Bartholinian gland, and therefore believe the following case worthy of record.

The patient came under my observation in July, 1928. She was then twenty-one years of age, single, born in the United States. Other than an appendectomy done seven years before to relieve intermittent abdominal pains, there was nothing important in the past history of moment. Following the removal of the appendix the abdominal pains continued, after which several different diagnoses were made to account for them. At the time of my first observation she reported to have lost in vitality and strength, becoming progressively worse each year although her appetite remained good. She stated that she was eleven pounds below her top weight. The abdomen presented a large, protuberant, diffuse mass occupying all of the area below the umbilicus. Temperature 101° F., pulse 90, white cell count 12,100, with 79 per cent polymorphonuclears. The patient being in marked distress, the abdomen was opened three days later and the appearance was that of an extensive tuberculous peritonitis. A thorough aeration was done and the abdomen closed. Moderate local improvement took place and four months afterward the condition had returned as before with three discharging sinuses of the tuberculous type in the scar. Several intraperitoneal injections of oxygen were given without any benefit, the entire abdominal condition finally clearing up with the intensive use of quartz lamp treatments, the sinuses also closing, and the woman remaining in good health ever since.

In April, 1934, there began a painless and noninflammatory swelling in the right vulva, no constitutional symptoms being connected with it. The only complaint was interference on sitting. The vulva in the locality of the Bartholinian gland on that side presented a cold, edematous swelling, extending from the perineum forward to about half of the vulva and up to the introitus. This was incised and a glairy, colorless, jellylike fluid discharged. Several days later the wound had healed and most of the swelling had subsided. Within a few days, the swelling returned about

as before and a second incision was done, the same sort of material obtained as before, and the wound packed. Quick healing of the wound permitted packing for only a few days. A return of the condition took place as before. Complete excision of the gland was then done, following which complete recovery took place.

The examination of the tissue removed was that of typical Bartholinian gland structure with considerable round cell infiltration throughout areas of the gland tissue. One minute tubercle was present, the central part of which contained a giant-cell and considerable protoplasm with a great number of nuclei arranged around its periphery. The tissue was not stained for tubercle bacilli but the pathology was definitely that of a tuberculous infection, which in view of the tuberculous character of the case and the clinical character of the local condition, warrants belief that a tuberculous infection of the Bartholinian gland can take place. Evidently the condition is very rare, and from the experience with this case, it would seem that when the condition exists, excision of the gland is essential for a cure of the condition.

RECURRENT HYDROCEPHALUS

H. R. Leland, M.D., Minneapolis, Minn.

THE occurrence of successive hydrocephalic children in the same woman is a very rare event and the paucity of such cases warrants this case report.

The patient, Mrs. A. G., aged twenty-two, married three years. Her mother had three children, all normal. The grandmother had 10 children, all normal. A sister had one child which was normal. On her husband's side, his mother had 4 children, all normal and his grandmother had 2 children, both normal.

The menses had always been irregular, four- or five-day flow, no pain. Her first pregnancy resulted in a breech presentation with perforation of a hydrocephalic head and delivery. There was a normal puerperium. The second pregnancy occurred one year later. All findings, including the laboratory, were negative except that the abdomen, on palpation, revealed an excessively large head over the pelvic brim. This was verified by x-ray examination to be hydrocephalic. She delivered a second hydrocephalic child which lived two months.

MUCUS TRAP FOR TRACHEAL INSUFFLATION IN NEWBORN INFANTS MODIFIED FOR THE ADMINISTRATION OF OXYGEN AND CARBON DIOXIDE

MELVYN BERLIND, M.D., BROOKLYN, N. Y.

A MODIFICATION of the mucus trap for tracheal insufflation in the treatment of asphyxiation in the newborn is here presented. The change consists in the addition of an extra inlet for the purpose of administering oxygen and carbon dioxide during the insufflation. The percentages used are 95 per cent oxygen and 5 per cent carbon dioxide, although straight oxygen might also be used.

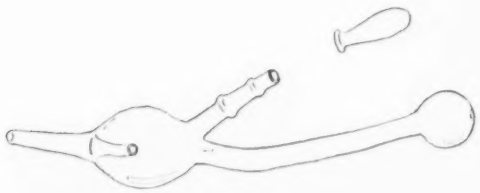

Fig. 1.

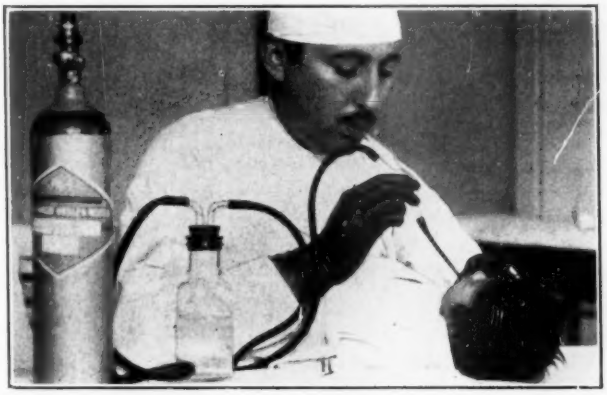

Fig. 2.

The advantages of this mucus trap appear obvious. It allows a high percentage of oxygen to come in direct contact with the pulmonary alveoli and thus very rapidly to decrease the primary cyanosis. The pressure under which the oxygen and carbon dioxide mixture is given can be gauged by the bubbling in the water bottle; a safe speed is approximately 100 bubbles per minute. Should the mucus trap be used without the oxygen-carbon dioxide tank, a nonperforated rubber nipple could be placed over the extra inlet. The catheters used are Nos. 10 and 14 French for premature and full-term infants, respectively.

My experience has been that the asphyxiated babies breathe earlier, with greater ease, and there is a marked and lasting improvement in their color with the addition of the oxygen and carbon dioxide. On occasion, I believe, it may be the factor in aiding to turn the scales in a seriously asphyxiated infant.

The mucus trap can be obtained from Eimer and Amend, New York.

125 Eastern Parkway

ROTRACTOR OBSTETRIC FORCEPS

M. Norman Moss, M.D., St. Paul, Minn.

IN GOING over the literature on old, new, and modified obstetric forceps, one wonders whether it is possible to devise a new forceps or improve on an old one, without infringing on one which has already been described before.

In the May, 1928, issue of this Journal I described a cephalic rotating forceps. The instrument was purely a rotator and recommended in transverse arrest of the head and posterior positions, to help bring the head into a more favorable diameter for final extraction with the regular Simpson forceps. It was the usefulness of this instrument, which prompted me to seek a forceps capable of combining the function of rotation with that of traction. The instrument described herein, is the end-result of that effort.

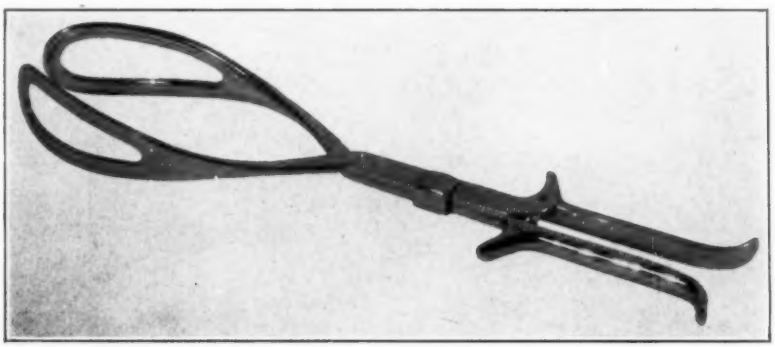

Fig. 1.

As one may observe from Fig. 1, the cephalic curve remains the same, while the pelvic curve is completely eliminated. The anterior and posterior edges of the blades are identical in every respect, thus permitting either blade to be inserted first and rotation made in either direction, without danger of gouging the ends of the forceps into the soft parts of the pelvis. The handles are identical to those of the Kielland forceps, being lighter in construction and much longer than those of the Simpson forceps. This feature is desirable, because it makes the instrument far more efficient in higher applications, as is usually the case in abnormal positions of the head.

Before making an application of the forceps, one must be positive of the exact position of the head, the membranes must be ruptured and the cervix completely, or nearly so, dilated. The hand is inserted and brought to the parietal side of the head and the blade is guided into position at this point. With the same hand still in the same position, the other blade is now inserted in the same manner and by means of the fingers guided around to the opposite side of the head. The blades

are now locked and gentle traction as well as slow rotation is made, both at the same time (corkscrew maneuver). When the occiput is brought into the anterior position and down to the pelvic floor, traction is continued in a straightforward direction instead of upward, as one usually does with the regular forceps. This latter change in direction of pull is necessary because of the fact that the rotractor has no pelvic curve.

During the past year, the rotractor is the only forceps I have used for instrumental delivery of any type. I have found it just as efficient in cases where the Simpson forceps is usually employed, but of utmost value in posterior positions and in transverse arrest of the head.

NEW LOWRY MEDICAL ARTS BUILDING

RECURRENT TUBAL GRAVIDITY ON THE SAME SIDE

JOSEPH DEUTSCH, M.D., AND JACOB CLAHR, M.D., NEW YORK, N. Y.
(From the Departments of Surgery and Pathology of the Morrisania City Hospital)

RECURRENT tubal gravidity on the same side is a very rare occurrence. This case is the only one encountered at the Morrisania City Hospital since July, 1929, during which time 88 patients with ectopic gestations were admitted. A complete study of the literature was made by Hasselblatt[1] in 1926, from which he was able to collect 19 cases, plus the addition of two new cases of his own. In his article he gives a summary of each of the 21 cases, and since they are for the most part similar to ours, it will be needless to quote his presentations. We have further reviewed the literature and found 8 additional cases,[2] 3 of which were interstitial tubal pregnancies and 5 in other portions of the tube. In this entire group of cases we also found two patients who had a triple occurrence of tubal pregnancy. The frequency of interstitial pregnancy (3 out of 8 cases) is quite common. It is important to note the associated absence of vaginal bleeding, which though not constant, is characteristic of the interstitial type. This is mentioned and emphasized by McIntyre,[3] Robinson,[4] and Vineberg.[5]

Our patient, a white woman, aged twenty-seven, married, was admitted to the Morrisania City Hospital Sept. 5, 1933, with the chief complaint of "pain in the lower abdomen and the right shoulder." Four days before admission, the patient noticed a lump in the lower right abdomen, which was tender to the touch, but not painfully so. On September 5, while being examined by her physician, vaginally, she complained of intense cramplike pains across the lower abdomen and fainted. Subsequently this pain radiated to the right shoulder. She was sent into the hospital, from the doctor's office, in shock.

This patient has been pregnant three times, twice delivered at term, and once operated upon for an ectopic gestation. Menses started at the age of fifteen years, occurred every three to five weeks and lasted seven days. Her last regular period was July 22, 1933. For two days prior to admission she had been spotting.

The patient was operated upon Dec. 18, 1931, for an ectopic pregnancy of the right tube. The right tube was removed at that time apparently leaving behind the interstitial portion.

Examination on admission revealed a pallid woman in shock with a pulse almost imperceptible. Her lower abdomen was tender and distinctly resistant, more emphatically on the right side. Rebound tenderness was marked. Vaginal examination revealed a mass in the lower right quadrant, filling the right fornix. The cervix was extremely tender on manipulation. There was no mass palpable in the culdesac.

The patient was treated for shock. It was noted that lowering the head of the table caused an exacerbation of the pain in the right shoulder. Fowler's position gave her more relief. A transfusion of 400 c.c. of whole blood was given before operation.

The blood count before operation was 23,000 white blood cells with 88 per cent polymorphonuclears and 12 per cent lymphocytes; 3,900,000 red blood cells and 85 per cent hemoglobin. The urine was negative.

The patient was operated upon soon after admission to the hospital under ether anesthesia. A median suprapubic incision was made, removing the old scar. The peritoneal cavity was found to be filled with blood clots. A large amount of this was removed. The uterus was brought through the wound and found to be slightly enlarged. A ruptured ectopic gestation was found located in the right cornua of the uterus. The tube iself was absent. The right ovary was adherent to the interstitial portion of the right tube. The left tube was normal and the corresponding ovary contained a corpus luteum vera. The cornua of the uterus containing the ectopic gestation including the ovary was removed by excision. The area was then closed by continuous suture and peritinealized. The abdominal wall was closed in layers in the usual fashion.

The patient made an uneventful recovery and was discharged on the tenth day postoperative.

Examination of the removed tissue disclosed an ovary closely adherent to the excised cornua of the uterus, which measured 2.5 cm. in circumference. It was smooth on its surface and contained many small cysts varying in size from a pinhead to 3 mm. in diameter. The mesial portion of the ovary was hemorrhagic and formed part of the wall of the ectopic gestation. The excised cornual portion of the uterus was also round and after fixation measured 3 cm. in diameter. It presented a ragged opening on its anterior wall which measured 1.5 cm. in diameter. Through this opening a very early placenta protruded containing an umbilical cord. On cut section the lumen of the tube was found to be dilated to 2 cm. in diameter with its wall measuring ½ cm. in thickness and its inner surface irregular and hemorrhagic. The uterine end of the interstitial portion of the tube did not contain its lumen.

Microscopic examination of the ovary disclosed several normal graafian follicles, engorged vessels, and enlarged stromal cells resembling decidual cells. Section through the placenta presented normal villi covered by a double layer of trophoblastic cells. The tube was made up of swollen muscle cells invaded by chorionic villi, chorionic wandering cells, and masses of trophoblastic tissue.

In our case the ovum came from the opposite side. It may have passed normally down the left fallopian tube, become fertilized, and entered the uterine orifice of the right tubal stump; this is extremely improbable. It is far more likely that the ovum, originating from the left ovary, crossed the peritoneal cavity and found its way into the tubal stump, which had regained its patency.

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1136 Teller Avenue

15 Clarke Place

SUPERNUMERARY MAMMARY GLAND TISSUE ON LABIA MINORA

WILLIAM F. MENGERT, M.D., IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology, State University of Iowa)

THOUGH accessory breast tissue has been known to occur on almost every part of the body surface, the appearance of bilateral mammary gland anlage on the labia minora seems out of the ordinary.

Mrs. G. S. (Hospital Number D-1250), aged twenty-four, gravida 5, was admitted to the Obstetrical Service of the University Hospital on May 30, 1929, about two weeks from the expected date of confinement. The pregnancy had been completely normal except for a mild hypochromic anemia. At routine antepartum examination, a soft, spherical, semicystic mass about the size of a plum stone was noted in the right labium minus adjacent to the clitoris (Fig. 1). A similar lump about half as large was present in the left labium. There was no inflammatory reaction. A

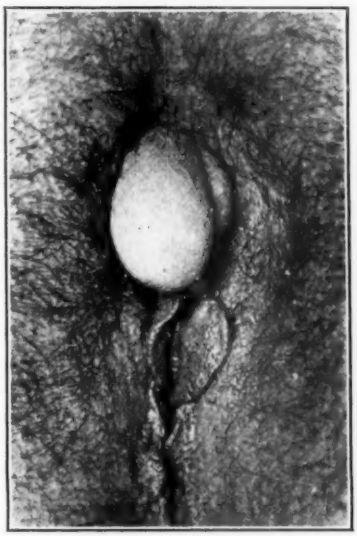

Fig. 1.—Photograph taken seventeen days postpartum. At this time the nature of these masses was not known. They were removed the following day.

provisional diagnosis of lipoma of the vulva was made. The patient had a spontaneous labor on June 10, 1929, giving birth to a normal male child. No further attention was given to the vulval masses until June 27, 1929, when the mass on the right measured 2 cm. and that on the left 1 cm. in diameter. The following day they were removed under general anesthesia.

Pathologist's Report.—"The tissue for the most part is glandular, which is separated into lobules by fibrous connective tissue. Two of the sections are covered on one side by a layer of stratified squamous epithelium in which an occasional hair follicle is seen. The acini vary much in size. Many are dilated, forming cystic

cavities in which a light staining material is found. The gland cells are cuboidal and are low cuboidal in the larger alveoli. The nuclei are large, ovoid, and vesicular. The cytoplasm contains droplets of fatty material. An occasional alveolus is found in which a second layer of cells is found forming a basement membrane. The nuclei of these cells are spindle shaped and resemble involuntary muscle. Diagnosis: Breast tissue, supernumerary.'' (Fig. 2.)

The report aroused so much interest that additional information was sought concerning the history of these accessory breasts. The patient stated that they were

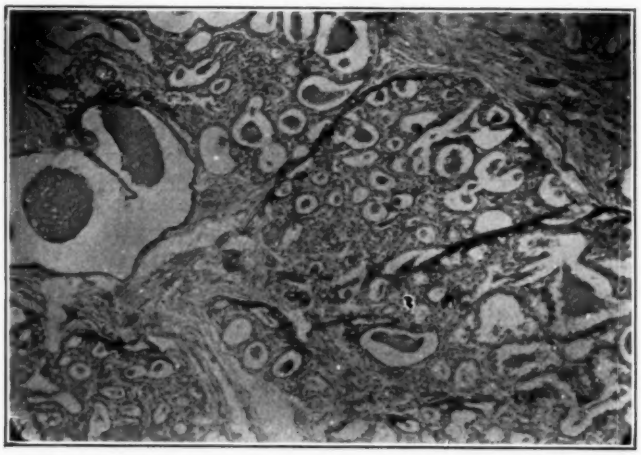

Fig. 2.—Photomicrograph of sections of the right labial tumor shown in Fig. 1. Note the secretion in the dilated, cystic acini.

not noted during the first three pregnancies, but that during the second month of the fourth pregnancy her family physician noticed a swelling near the clitoris, and in the fourth month the patient noticed it herself. The lump gradually became larger until delivery, following which it was tense and painful for about four days and then subsided to become impalpable. During the present pregnancy it followed a similar course.

Petit-Dutaillis, P.: The Value of Weight in the Detection of the Arrest, Persistence or Recurrence of an Epithelioma of the Cervix After Treatment, Gynécologie **32**: 193, 1933.

It is generally accepted that recurrences of carcinoma more than five years after treatment are extremely rare. But it is a mental hardship for a woman or her family to wait five years to be sure of a cure. Most individuals would like to know the prognosis long before the five-year period has elapsed. Petit-Dutaillis is of the opinion that in the weight of the patient we have a reliable index of the success or lack of success in therapy. A weight chart must be kept, beginning at the time the treatment is begun. The weight should be taken regularly once a month under approximately the same conditions. If a woman gains in weight after treatment, the cancer is not progressing or there is not a recurrence. The more the gain in weight and the more rapidly this takes place, the more favorable the prognosis.

J. P. GREENHILL.

PROLONGED RETENTION OF FETUS FROM AN EXTRAUTERINE PREGNANCY

T. H. Aschman, M.D., and F. C. Helwig, M.D., Kansas City, Mo.
(Departments of Obstetrics and Pathology, St. Luke's Hospital)

MANY amazing instances are on record of prolonged retention of an extrauterine pregnancy and there are records of successive pregnancies during such retention. The ultimate fate of the retained fetuses is likewise a matter of considerable interest. After a certain period of gestation, the fetus cannot be absorbed after it dies, and hence with the entry of microorganisms may undergo secondary infection, suppuration, and even partial autolysis. The infected parts may necrose into the bowel or even through the abdominal wall and be thus expelled if the patient does not succumb to the infection. Sometimes these fetuses become mummified or calcified and at times may even undergo adipocere degeneration.

Case 1.—Mrs. W., aged sixty-nine, entered the hospital because of pain and enlargement of the abdomen of about three months' duration. The pain started in the lower abdomen and gradually became more or less generalized. She had had trouble with "bloating" for about nine months prior to her hospital admission. The history was otherwise negative except for the statement that thirty-five years previously she had a miscarriage and was never again pregnant.

Examination showed an enlarged, dense, tympanitic abdomen with a definite fluid wave. Roentgenographic examination revealed inadequate filling of the cecum, many diverticuli in the descending colon, and a calcified mass about the size of a grapefruit in the left lower quadrant. This calcified mass was removed and at this time considerable fluid was found in the abdomen. Although at operation a possible carcinoma of the cecum was suspected, none was found. The patient continued with her former symptoms and had considerable vomiting. Another exploratory laparotomy was performed and about two-thirds of the stomach was found to be involved by a large carcinoma, which extended into the head of the pancreas. Omental metastases were found to be partially obstructing the middle portion of the ascending colon. The patient subsequently left the hospital and no later history was obtained.

Pathology.—The specimen was a heavy semicalcified, more or less spherical, tumor mass, rusty brown in color and covered with shaggy adhesions. It measured 11 by 9 by 9 cm. and on cross-section it was extremely difficult to cut. Masses of hair, skull and fetal parts presented themselves and intact arms and legs were readily discernible. This tumor when first examined was thought to be a calcified dermoid cyst and was so diagnosed. When the second case was observed, however, the similarity of the two specimens was so striking that this tumor was re-examined and roentgenograms revealed the bony skeleton and partially intact fetal parts.

Case 2. Mrs. M., twenty-four years of age, was seen by one of us (T. H. A.) when admitted to the Kansas City General Hospital complaining of pain in the right side. She was apparently threatening to abort. She gave a history of having had gonorrhea the past four years. Her last normal period was six months previously. At the next period she flowed only about fifteen minutes and from this time on she had a tendency to flow for about ten or fifteen minutes every time she did any heavy lifting. Four months after her last period she had a large flow with

sharp pains in the right side. She had fainted several times and had aching in the right side, which symptom, however, had been present more or less all of her life. For the past four months she had had some flowing after any type of moderately strenuous exercise. For the first three months of her supposed pregnancy, she had nausea and vomiting; and at the fourth month felt movement, which continued until one week prior to entry in the hospital.

Examination at this time revealed a tumor mass rising two fingerbreadths above the umbilicus and "a placental souffle was heard over the pubis" but the fetal heart was not heard. The impression at this time was that of a six months' pregnancy with a possible dead fetus. A roentgenogram taken at this time to rule out abdominal pregnancy was recorded as "skeletal structure of fetus with head on the right side. The outline of the fetus is visible along the lateral margin. This is an intrauterine pregnancy" (Fig. 1). Vaginal bleeding ceased about the third day

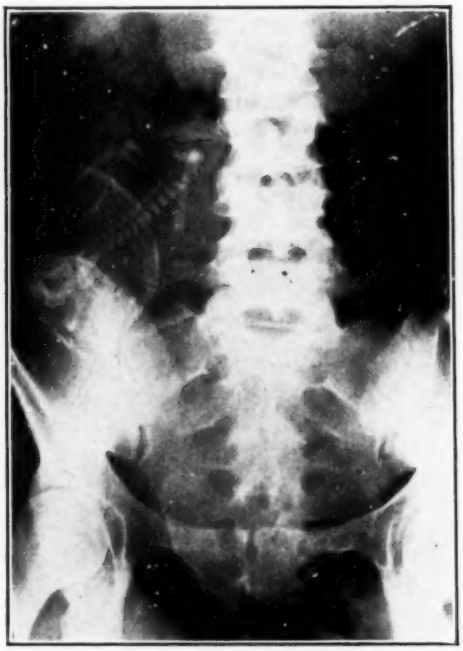

Fig. 1.—Case 2. Roentgenogram erroneously diagnosed as "intrauterine pregnancy."

but pain at intervals continued in the right lower quadrant. The patient was then dismissed from the hospital on the ninth day and instructed to report to the Out-Patient Department; this she failed to do.

At the expected time the patient did not go into labor and the abdomen seemed to decrease in size. Her periods became normal every twenty-eight days and she consulted a physician who told her she was not pregnant but that she had a "fibroid tumor." She, therefore, returned to one of us (T. H. A.) six months after her first admission, or one year after she missed her first period. At this time, a pelvic tumor was found which was about the size of a grapefruit. It was hard and nodular in character and it was thought to be either a fibroid or perhaps a calcified intrauterine fetus. Operation was advised and the patient entered St. Luke's Hospital for operation three months later. A large mass was found in the right pelvic cavity which was enclosed in a membranous capsule. This mass and the appendix were removed and the patient had an uneventful convalescence.

Pathology.—The mass was covered with a grayish membrane and the entire specimen weighed 546 gm. The mass of sac and fetus was irregularly rounded and seminodular in shape and measured 14 by 10 by 7.5 cm. Fetal parts were easily palpable through the sac walls. On opening, no fluid was present in the sac. The fetus was mummified and dehydrated but all parts were easily identified.

Two cases of long retained extrauterine pregnancy are here recorded. One was possibly of thirty-five years' duration and was discovered in the roentgenogram as a pelvic tumor and removed during an exploratory operation for cancer of the stomach. On gross examination, it was considered to be a calcified dermoid but later dissection and roentgenograms revealed well-formed, skeletal parts in spite of the long retention. The second case was of fifteen months' duration, had been erroneously diagnosed as intrauterine pregnancy both clinically and from roentgenographic examination, but when the expected delivery failed to transpire a retained pregnancy was suspected which, on subsequent operation, proved to be extrauterine.

PLACENTA PREVIA COMPLICATING TWIN PREGNANCY

M. W. Haws, B.S., M.D., Fulton, Ky.

IN THE August, 1934, issue of this Journal, Gallagher-Heaton reported a case of twin pregnancy complicated by placenta previa. Seeing the following case a few days after receiving the Journal stimulated my interest in this complication. In a rather hasty survey of the literature and after searching through three textbooks on obstetrics, I was unable to find any mention of a special way to handle these cases. I wish to add the following case of single ovum twins complicated by placenta previa.

Mrs. D. W., white, wife of a farmer, aged thirty-one, was admitted to the hospital Oct. 11, 1934, at 12:30 P.M. The patient was a para vi, having had four normal pregnancies and one five months' abortion; one and a half year previous to this pregnancy the patient had always enjoyed good health, except for childhood diseases. There was no history of twin pregnancies in either family of the wife or husband. The patient's menses began at the age of eleven, were regular, 28-day type and painless.

I saw the patient first in my office, July 6, 1934. At this time her blood pressure was 115/80 and urine negative; last menses occurred March 18, 1934. Estimated date of delivery being Dec. 25, 1934. In my neighborhood we have some difficulty in seeing our patients regularly; although this patient was urged to report monthly, I did not see her again until about 11:00 A.M., Oct. 11, 1934. At this time I received a hurry call to the patient's home. She gave a history of painless bleeding for about ten days, but because of her previous miscarriage thought very little about it. About half an hour before my arrival there had been a painless gush of blood. When I arrived, the patient was pulseless, very pale, and blood was flowing freely from the vagina. Being sure I was dealing with a placenta previa and seeing the patient was in extremis, I immediately packed the vagina, under as clean conditions as possible. The pulse could not be felt and the blood pressure reading could not be obtained. The pack controlled the bleeding and the patient was sent to the hospital at once.

On arrival at the hospital, the packing was removed and the patient examined. The diagnosis of partial placenta previa was confirmed, the placenta being on

the left side posteriorly, and only a small part extended over the cervix. The cervix was half effaced and dilated so that two fingers could be inserted. As the examination excited more bleeding and the patient was already in extremis, a No. 6 Voorhees' bag was hastily inserted and the vagina packed tightly. Patient was returned to bed at about 1:00 P.M. Blood pressure was still zero and no pulse could be felt. Intravenous saline with 5 per cent glucose was started and the patient was given 2,500 c.c. by 4:00 P.M. Donors for a transfusion were searched for but none would match.

At 4:00 P.M. the blood pressure had come up to about 50 and a small pulse could be felt at the wrist; red blood cells numbered 1,750,000 and 35 per cent hemoglobin. Patient had no pains after her return to bed, but due to the questionable conditions under which the first pack was inserted, and fear of infection, it was thought advisable to deliver her as soon as possible; hence she was returned to the operating room at 4:15 P.M.

On removal of the pack and bag, it was found that the cervix would accommodate four fingers with some little difficulty. The membranes were unruptured, and the baby was presenting by vertex. When the packing was removed bleeding recurred, so under a light ether anesthetic, we started to do a version and slow extraction. The membranes were ruptured and the posterior foot brought down. The version was easily completed, and we were greatly surprised when no resistance was offered to the birth of the baby, which was completed immediately. The baby weighed 2½ pounds, and made no attempt to breathe. Up to this time there was no suspicion of a twin pregnancy, but after the delivery of the first small baby, my suspicions were aroused. On palpating the uterus, which was still well above the umbilicus, another baby could be distinctly felt. The hand was reinserted into the uterus, the second membrane ruptured, and the second baby, weighing 2¾ pounds, was delivered easily by version and extraction. This baby also made no attempt to breathe. During these manipulations a small amount of bleeding had occurred and the patient had again become pulseless, so immediately following delivery of the second baby, the hand was reinserted and the placenta delivered manually in order to hasten the return of the patient to bed. After delivery of the placenta, 1 c.c. of pituitrin was given, the uterus contracted firmly, and there was no more bleeding. Patient was quickly returned to bed at 5:00 P.M. and given another 1,000 c.c. of saline and 5 per cent glucose.

By 8:00 P.M., one was able to feel a feeble pulse at the wrist, and the blood pressure registered 60/0. A continuous hyperdermoclysis of normal saline was continued through the night, and by 7:00 A.M., the next morning the pulse could be counted at 135 and blood pressure registered 105/70. The patient ran a temperature between 99° and 102° from the second to the seventh day, but otherwise made an uneventful recovery, and was up doing her work in three weeks.

Society Transactions

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 7, 1934

The following papers were presented:

Chorionepithelioma With a Long Latent Period. Dr. David Feiner. (See page 840.) Discussed by Dr. S. A. Wolfe.

The Pelvic Fascia. Dr. Nathan P. Sears (by invitation). (See page 834.) Discussion opened by Dr. O. P. Humpstone.

Dougal, Daniel: Ovarian Conditions as Causes of Pelvic Pain, Brit. M. J. **2:** 621, 1934.

The author describes ovarian pain as one of the "bugbears" of medical practice. True ovarian pain is splanchnic and apparently of a low order; reflected superficial pain of ovarian origin only occurs when the parietal peritoneum is irritated by the ovary. Ovarian conditions producing pelvic pain may be grouped under four headings: functional, mechanical, inflammatory, and neoplastic.

In discussing the functional disturbances, pros and cons are given concerning the possible etiologic bearing of cirrhosis and sclerocystic disease of the ovary as well as of ovarian dysmenorrhea. In treating this group of disturbances, mention is made of excision of ovarian nerves in the hilum of the ovary as well as of organotherapy.

In discussing mechanical disturbances of the ovary, the author regards prolapse of the ovary generally beneath a retroverted uterus as most common and also mentions varicocele of the broad ligament and torsion of the ovarian pedicle.

Inflammatory disturbances of the ovary usually follow a salpingitis when the ovary becomes adherent to the neighboring structures. Pelvic peritonitis may be an associated causal factor of pelvic pain.

In conclusion, the author states that while neoplasms of the ovary are practically painless unless torsion, degeneration or infection occurs, endometrioma is an exception because by its adherence it causes stretching of the ovary from effused menstrual blood and also causes irritation of the nerves in the broad ligament and of the parietal peritoneum.

F. L. Adair and I. C. Udesky.

American Journal of Obstetrics and Gynecology

EDITORS: GEORGE W. KOSMAK, M.D., AND HUGO EHRENFEST, M.D.

Editorials

Present Status of Endocrinologic Diagnosis and Treatment

NO BRANCH of medicine during this century has made such enormous strides as endocrinology. This impetus was given by gynecologists and obstetricians including Fraenkel, Fellner, Ockinschitz, Herrmann, and Halban, in the years from 1903 to 1917. Surgeons, particularly Cushing, and also a gynecologist, Aschner, were among those who initiated the studies on the pituitary. The ever-increasing elan of endocrinology has enlisted assistance from all directions including internists whose accurate observations on various symptom complexes have been invaluable. Pathologists, physiologists, biochemists, and organochemists as well as physicists have performed important work in this field.

In consequence of this mass work, many dark and uncertain phases of medicine have been illuminated, but much still remains to be clarified.

The rapid advance has left the subject in the chaotic state of a new mining camp before law and order has been introduced. Wheat and chaff have not been separated. Innumerable reports of isolated observations are confusing even to the initiate, so that the average practitioner in despair frequently turns to the advertising literature and the detail man for information, which at least is positive, clear-cut, although often erroneous.

In trying to evaluate, particularly, the therapeutic weapons at our disposal, three types of results are apparent.

The first is clear-cut and unmistakable, such as the effects of thyroid preparations and insulin.

The second, remedies which are biologically assayable in the laboratory and give fairly concordant results when applied to the patient, such as the effect on the calcium metabolism produced by parathyroid extract or the relief of "shock" in Addison's disease obtained by *potent*

extracts of the adrenal cortex, and here the word of warning issued by Rogoff* as to the lack of value of many of these preparations is pertinent.

The third includes the large number of preparations which exert assayable influence on laboratory animals but whose clinical effects either are unconvincing or allow of many interpretations.

This latter group is of particular interest to the gynecologist and obstetrician, as in it are included the prepituitary and prepituitary-like hormones, the estrogenic and corpus luteum hormones. On laboratory animals the bio-assay is convincing. On the human being the results are no more striking and concordant than in the days when patients were given desiccated ovarian and pituitary preparations, which increase in our knowledge has shown were devoid of any physiologic effect.

Of all the patients treated with this type of endocrine products, only two groups permit of any critical analysis: the sufferers from *dysmenorrhea* and the *menopause*. It is essential to exclude both amenorrheas and meno- and metrorrhagia from a critical and objective review, for, as is well known, return to normal function takes place in so many instances without detectable change and without any endocrine or other therapy, that observations based upon these groups must be thrown out of court. There are records available of many cases where primary amenorrhea, as well as excessive bleeding, extending over periods of many years and where long courses of "treatment" have proved ineffective, spontaneously recover.

Allowing for this possibility of error, one still might be convinced by sufficient statistical proof of carefully studied and large groups of patients, if the results of many observers were concordant. But they do not tally. It is striking and significant that usually those authorities who in years gone by obtained gratifying results with remedies, which we now know were biologically inert, are the ones who today again herald their therapeutic triumphs by the use of newer drugs. This need not imply bad faith but merely lack of critical judgment.

Even when dealing with such definite symptoms as dysmenorrhea, great caution must be exercised. Let us remember that the stem pessary, dilatation and discission of the cervix, the Dudley, Pozzi and Blair Bell operations, cauterization of the nasal spots, benzyl benzoate and other remedies, have been lauded, accepted, and discarded in turn. The same applies to the cure of menopause symptoms, where ovarian desiccates, ovarian residue, desiccated corpus luteum extracts, estrogenic hormone have been hailed as panaceas but have not stood the acid test of continued trial.

The causes which produce dysmenorrhea and the menopause syndrome are not understood. There is evidence to support the thesis that the symptoms may be due not to one but to several basic disturbances, to

*Rogoff, J. M.: J. A. M. A. **103**: 1764, 1934.

over- as well as to underproduction or possibly to failure of interaction of various hormones. The indecent haste with which certain clinicians inject into their docile patients the latest hormonal fraction, whether obtained from pregnancy urine, the ovarian follicle, the thymus, the middle lobe of the pituitary or the placenta, is revolting. The conclusions they draw are equally hasty and unreliable. Next month or year they will be off on another tangent with undiminished enthusiasm and optimism.

The prospect that eventually hormone therapy of gynecologic and obstetric functional disturbances will be put on a rational and effective basis is excellent. Such result will develop from well-selected, carefully controlled, and objectively studied series of cases; perhaps by trial and error, certainly not by machine gun type of endocrine drugging to which the profession is becoming addicted.

Robert T. Frank.

Certain Influences on Cancer Production

THE conflicting rôles of heredity and environment in the production of cancer have been in theory reconciled in a recent article by Lynch in the *Bulletin of the American Society for the Control of Cancer*. Her thesis is briefly that heredity may determine general susceptibility and even a predisposition to localization in certain organs, but that environmental factors will have a deciding influence on the final appearance of the growth in the available organ. Conversely, the effectiveness of an external agent to produce cancer is limited by a factor inherent in the constitution of the individual.

Many examples are found among the tumors of the female pelvis to illustrate these environmental and constitutional factors. Particularly in the glandular forms of carcinoma of the uterus and its appendages, evidences of constitutional and hence probably hereditary influences are important. Thus, there is the oft cited abnormality in onset of puberty and menstrual type and the relative infertility of women with certain types of adenocarcinoma of the uterus and ovary. Further evidence of a general predisposition is found in the common occurrence of multiple tumors, such as the coincidence of myoma and adenocarcinoma of the uterus and myoma with adenocarcinoma of the ovary. Spontaneous bilateral development of ovarian tumors and the appearance of multiple papillomas in independent locules of many ovarian cysts are further examples. The evidence of an at least "protective" effect of such an internal factor as the ovarian secretion is found in the atrophy of myomas and endometriosis after the normal or artificial menopause. Whether a

"causal" relationship exists, as recent studies have suggested, between certain pelvic tumors and dysfunctions of the ovary is not so well established.

The origin of the squamous type of cancer, that of the cervix and vagina in particular, appears more closely associated with environmental conditions, especially the chronic irritation accompanying laceration or infection. The occasional occurrence of cancer at the site of contact with a pessary is a less common, but striking, example of cancer from external sources. There is, furthermore, little tendency for these tumors to be multiple and locally acting forces appear therefore to play the predominant rôle.

After consideration of the specific functions of the various tissues of the pelvic organs, one is tempted to offer the hypothesis that the hormone controlled glandular tissues will yield tumors as a result of endogenous agents, possibly in the form of hereditary disturbances of function, while the squamous epithelium of the cervix and vagina will produce abnormal growth when its normal function, that of acting as a protective covering to the deeper tissues, is excited for a long period by chemical or mechanical irritants. There are, however, observations to upset such a clear distinction. Inflammatory factors are found in the adenomyosis of the uterine cornua and are suggested in certain cases of tubal and ovarian cancer and in the reported association of adenocarcinoma and tuberculosis of the endometrium. Furthermore, though chronic irritation may appear of paramount importance in cervical cancer, a constitutional factor is perhaps necessary to explain why one patient with a slightly diseased cervix will develop cancer while a hundred women will carry badly lacerated and infected cervices for years without the development of any neoplastic complication. A fine example of a combination of constitutional and environmental factors is found in the cancer of the vulva which may develop as a result of a chronic inflammatory condition in a preexistent leucoplakia, which itself may have a constitutional basis.

The neoplasms of the pelvis are in many ways particularly favorable for research. They are common and are easily obtainable in large groups. Historical data on the reproductive and menstrual functions and the symptoms of chronic infection are more accurate than for most other systems of the body. Pelvic tumors are, furthermore, for the most part fairly accessible to the examining hand or eye. Finally, the factors producing normal growth and atrophy are rapidly becoming better known and are more readily studied for this region than for any other in the body. The pelvis is, therefore, a most promising field for further study and one from which much may be hoped toward the ultimate solution of the problem of neoplastic disease.

Howard C. Taylor, Jr.

Department of Reviews and Abstracts

Conducted by Hugo Ehrenfest, M.D.

Selected Abstracts

Pregnancy Complicated With Diseases of Pancreas and Kidney

Rosenloecher, K.: Changes in the Pancreas During Pregnancy in Women and in Animals, Arch. f. Gynäk. **151:** 567, 1932.

The author made histologic studies of the pancreas of pregnant and nonpregnant animals and of women dying during or shortly after pregnancy. He finds a definite increase in the size and number of the isles of Langerhans. There is also an increase in zymogen granules. Changes in the pancreas are noted in the parenchyma as well as in the islands of Langerhans. Apparently the greatest increase in pancreatic activity occurs during the middle trimester of pregnancy and toward the end of pregnancy.

Ralph A. Reis.

Duncan, G. G., and Fetter, F.: The Effect of Pregnancy on the Insulin Requirement of the Diabetic, Am. J. M. Sc. **187:** 347, 1934.

Exact control of diabetes throughout the course of pregnancy will prevent abnormal demands on the pancreas of the fetus. By adopting such a practice the insulin requirement increases in the first trimester, remains constant in the second, increases in the third and decreases suddenly after delivery. Pregnancy under ideal conditions and proper treatment does not permanently impair the diabetic's tolerance. Diabetes by itself is not a contraindication to pregnancy.

J. Thornwell Witherspoon.

Eyding, A.: Diabetes and Pregnancy, Zentralbl. f. Gynäk. **57:** 514, 1933.

Three women with diabetes during pregnancy, coming under the author's observation in one year, are reported. In 2 of them, pregnancy was allowed to go to term. In the third woman pregnancy was interrupted because she also had hypertension and excessive adiposity. In the 2 women who went to term, the sugar tolerance increased as pregnancy neared the end, but dropped again after the baby was born. The typical complications seen in pregnant diabetics, namely, acidosis, hydramnios and excessive skin depot fat in the babies, were all noted in the women who went to term. Pregnancy is rare in diabetics, but the author thinks that a higher conception ratio is possible with the use of insulin. The value of operative delivery is questionable.

William F. Mengert.

Liebmann, S.: The Course of Diabetes Complicating Pregnancy and Labor, Monatsch. f. Geburtsh. u. Gynäk. **91:** 398, 1932.

Among 22,773 cases of pregnancy and miscarriage there were 12 women who had more or less severe, true diabetes (0.05 per cent), which expresses the infrequency of this ailment in pregnant women. Eight of these patients were seen before or at the beginning of the era of insulin. In only 4 cases was it thought advisable to interrupt the gestation. One patient died in spite of the therapeutic abortion. Most authors still favor interrupting the pregnancy in severe cases because of the seriousness of coma. Good results in diabetic pregnant women may be obtained by the use of a proper diet and insulin throughout gestation but when insulin is not administered until the patient is in coma, not much can be accomplished. It is generally believed that under proper management the life of a diabetic pregnant woman is not jeopardized and if proper precautions are taken labor and the puerperium are uncomplicated. However, extraneous circumstances may arise and lead to complications. Diabetic women should be delivered in a hospital. Pregnancy should be interrupted when there is a high degree of acidosis and especially when the ketonuria increases during pregnancy; when the sugar tolerance decreases and more and more insulin is necessary, and when any unlooked-for complications arise. In mild cases, when diet and insulin can maintain the proper sugar tolerance without much difficulty, the patient may safely nurse her baby.

J. P. Greenhill.

Bix, H.: The Relationship Between Maternal Diabetes and Giant Children, Med. Klin. **29:** 50, 1933.

Pregnancy in diabetic women is not common. If conception does take place the diabetes usually has an unfavorable effect on the fetus because abortions are frequent and children born at full term are weak and have a high death rate during the first few days of life. On the other hand, diabetic women not infrequently give birth to very large babies. The cause of this is considered to be the high blood sugar in the mother furthering the growth of the fetus. Bix investigated a series of 192 married diabetic women. Among this group 37 (19.4 per cent) had never been pregnant. The other 155 women had 608 children of which 63.3 per cent were of normal weight, 18.1 per cent weighed more than 4,000 gm., 7.7 per cent more than 4,500 gm. and 10.9 per cent 5,000 gm. or more. Hence more than 37 per cent of the children were overdeveloped. In an occasional case, a giant child was the first manifestation of a latent diabetes. Hence when a woman gives birth to an unusually large baby, a careful investigation should be undertaken to determine whether or not she has latent or active diabetes. Even if the findings are negative, the woman should be carefully observed for a long time afterward.

J. P. Greenhill.

Theobald, G. W.: The Relationship of the Albuminuria of Pregnancy to Chronic Nephritis, Lancet **1:** 626, 1933.

Bright's disease is causally associated with environment and heredity, but more intimately and predominantly with age. The following facts tend to prove that pregnancy and childbirth have relatively little causal association with chronic nephritis: (1) Mortality curves for women follow the same upward and downward trends as those for men; (2) mortality rates for Bright's disease are the lowest in rural districts in which those for albuminuria and convulsions are usually highest; (3) mortality among young widows is strikingly high; (4) there is very little difference in mortality rates for married and single women up to the age of 55.

The risks of marriage and childbirth are less than those of a spinster at any age after thirty years, while Bright's disease has a considerably higher mortality in single, than in married, women after fifty-five years. The author warns that chronic nephritis is too frequently charged to the so-called toxemias of pregnancy and implies that such views lead to an increase in the number of abortions and obscure the actual etiology of either "toxemia of pregnancy" or Bright's disease.

H. CLOSE HESSELTINE.

Batisweiler, J.: The Connection Between Premature Separation of the Placenta and Renal Disease, Arch. f. Gynäk. **153:** 536, 1933.

The author finds that renal disease of the type which may lead to anuria is frequently present in women in whom there is a premature separation of the placenta. This type of renal disease resembles interstitial nephritis with only slight degenerative changes. There is usually no edema and the blood chlorides are normal, but the rest—nitrogen and blood pressure are increased. Eclampsia rarely occurs. Chronic renal suppuration may be present or there may be marked edema of the interstitial portions of the kidneys.

The therapeutic problem remains unsolved. Decapsulation of the kidneys may be successful but is not in general use because of the seriousness of the procedure and because some failures have been reported. The author recommends the administration of large quantities of fluids (5 to 6 liters per day). These are given orally, rectally, subcutaneously and intravenously in order to keep the blood pressure high since maintenance of a high blood pressure is a protective mechanism against the development of anuria.

RALPH A. REIS.

Kellar, R. J., and Arnott, W. M.: Bilateral Cortical Necrosis of the Kidneys, Edinburgh M. J. **40:** 101, 1933.

Bilateral cortical necrosis is an uncommon but dramatic complication of pregnancy. With its principal clinical feature of extreme anuria and its characteristic gross pathologic features it provides a peculiarly precise syndrome.

In 40 of the approximately 50 recorded cases, the condition was associated with pregnancy. It shows no tendency to select the primipara and most cases are found in the twenty-five to thirty-five age period. It usually supervenes during the fifth, sixth or seventh month of pregnancy. Previous pregnancies are usually normal. The course of the pregnancy up to the onset of the condition may be quite uneventful but more usually there are disturbances indicative of a degree of toxemia. These may be hyperemesis, headaches, edema, dimness of vision, etc.

Some of the cases have been associated with eclampsia or some other toxic manifestation, such as concealed accidental hemorrhage, but in the majority the patient is more likely to come under notice because of vaginal bleeding or some sign of impending delivery.

The one invariable clinical feature is anuria. This may be absolute or may be an extreme oliguria. It may be of short duration or it may endure for the astounding period of twenty to twenty-five days.

The closing stages are marked clinically by progressive exhaustion and there may be some terminal infection. The classical symptoms of uremia such as amaurosis, periods of unconsciousness, severe convulsions, etc., are usually absent. The blood pressure is usually normal. Edema is frequently present although it is not a prominent feature.

The kidneys as seen at autopsy are very slightly, if at all, enlarged. These necrotic areas show a hyaline necrosis. A fairly constant feature is the presence of thrombosis in the intralobular vessels and in the afferent glomerular vessels. The presence of fat globules in the vessels is an expression of the hyperlipemia.

Treatment to be rational must follow the pathologic picture assumed to be present at any particular state of the illness. Thus, in the early stage, the indication would seem to be to relieve the congestion in the kidney substance and thus allow the nonnecrotic areas the best chance of survival. It is a point of nice judgment whether decapsulation should be attempted.

WM. C. HENSKE.

Fuller and Colebrook: Treatment of Urinary Infections in the Puerperium by a Ketogenic Diet, Lancet **2**: 735, 1933.

It is difficult to evaluate how much the pyrexia in puerperal infection is influenced by an associated urinary tract infection. Until 1932 the urinary tract infections were treated along "conventional lines" using fluids, large doses of potassium citrate and occasionally, in the more severe ones, acriflavine or some other urinary antiseptic. Since then the ketogenic diet has replaced nearly all therapy; and in general, this diet is well tolerated if it is made as palatable as possible and the patient cooperates. Three or four of the patients had such nausea and vomiting that the diets had to be discontinued. The stricter the diet the greater the output of beta-oxybutyric acid.

Twenty-four of the 54 patients had sterile urine in seventeen days; patients infected with cocci responded more quickly. No explanation is offered for the failure to produce even a moderate ketosis in 22. The diet had been discontinued within forty-eight hours after the urine became sterile, which might perhaps be unwise.

The dietary employed and the method of determining the degree of ketonuria is described.

H. CLOSE HESSELTINE.

Stark, E.: The Treatment of Pyelitis With Special Consideration of Irrigation of the Kidney Pelves and Retention Catheters in the Ureters, Monatsch. f. Geburtsh. u. Gynäk. **94**: 29, 1933.

In a series of 72 cases of pyelitis only 59 were successfully treated by general medical measures. In 13 cases local treatment had to be instituted. In 3 cases the renal pelvis had to be irrigated, but no retention catheters were used. In 8 cases retention catheters were employed with and in 2 cases without renal pelvic lavage. The patients whose renal pelves were irrigated but not drained by indwelling ureteral catheters required a longer time for a cure. Ureteral catheterization removes the primary etiologic factor, namely stagnation. In the cases where drainage for thirty-six to forty-eight hours and irrigations were used, medical therapy was also employed in conjunction. The pain which was produced by spasm of the ureter as the result of the foreign body in the ureter was overcome by pantopon. Local treatment was only instituted when medical therapy failed. When pelvic irrigations and ureteral drainage do not give relief, there is usually some complication present such as renal tuberculosis, stone, perirenal abscess, etc. During pregnancy, especially when pyelitis is associated with constipation, relief may be obtained by high intestinal irrigations.

J. P. GREENHILL.

Correspondence

The Treatment of Gonorrheal Vulvovaginitis of Childhood with the Ovarian Follicular Hormone

A Series of Unsuccessfully Treated Cases

To the Editor:

The treatment of vulvovaginitis in infants and young girls has always been an unsolved problem. The various methods of therapy have offered so little encouragement in the eradication of this disease that it was with great enthusiasm and with a warm reception those of us who contact this condition welcomed the very rational hormonal therapy first advanced by R. M. Lewis in 1933. His results were so encouraging that many clinics undoubtedly began immediate application of his treatment.

After one year's investigation of this therapy, the results from Tulane University Clinic, unfortunately do not substantiate Lewis' findings.

As far as can be discovered this is the first unfavorable report to be offered dealing with this method of therapy. Ten patients between the ages of two and ten years have been given daily (with an occasional Sunday exception) doses, 1 or 2 c.c., 50 or 100 R.U. of amniotin (E. R. Squibbs & Sons) over a period of forty-two to ninety-two days. The amount of discharge was generally lessened with the prolongation of the treatment, although several cases exhibited exacerbations and remissions of flow. Weekly vaginal smears were made with Gram stain and in only one case were no intracellular gram-negative diplococci observed after sixty-six days of treatment. This case later exhibited a positive smear while still under treatment. The remaining 9 cases continually presented a positive gonococcal smear. The smears in every case showed many desquamated epithelial cells, suggesting conversion of the infantile vaginal epithelium into the more mature adult type. In no case can we say a cure was effected, and finally, due to the exhaustion of patience of both parents and children, the former treatment of vaginal irrigations was resorted to.

One observation noted in Lewis' series was the rapidity (ten days) with which cures were effected. The knowledge we have acquired of this disease through handling two other groups of patients impresses us very forcefully with one feature of this condition, the chronicity of the disease. Such rapid cures seem all too utopic in face of our previous experience.

There are several arguments, both theoretical and practical, against this method of therapy. The most important consideration is whether or not the administration of the ovarian follicular hormone to young girls is harmful to their later development. Even though such eminent observers as Allen says to the contrary, we feel the weight of evidence is in favor of inhibition of mature ovarian development, with subsequent atrophic and fibrotic changes in the ovaries.

A second argument against this method of therapy, from a more practical viewpoint, is that in many cases of vulvovaginitis the infection is not limited just to the vaginal mucosa, but involves the cervix as well. In such cases the cervix must

be actively treated or else the resultant cervicitis, even though the vulvovaginitis is cleared by hormonal therapy, will remain as a focus of infection from which the disease could persist.

Another unpleasant feature of this therapy is the technic of administrating the hormone, the daily hypodermic injection. When the novelty of the treatment wears off, the daily visit to the clinic, by parent and patient, to be "stuck," becomes a very definite problem.

TABLE I

AGE	DURATION OF DISEASE	AMOUNT OF DISCHARGE	VAGINAL SMEAR AT ONSET	DURATION OF TREATMENT	DAILY DOSES	SMEARS AT END OF ONE MONTH	TWO MONTHS	THREE MONTHS	SMEAR AT END OF TREATMENT	LOCAL REACTIONS
9	Birth	Heavy	+	42 d	50 R.U.	+			+	0
6	9 mo.	Mod.	+	82 d	50 and 100 R.U.	+	+		+	Pain
10	9 yr.	Heavy	+	50 d	50 and 100 R.U.	+			+	0
2	2 wk.	Heavy	+	50 d	50 and 100 R.U.	+			+	0
4	1½ yr.	Mod.	+	42 d	50 R.U.	+			+	0
9	1 yr.	Heavy	+	92 d	50 and 100 R.U.	+	+	+	+	Pain
7	2 yr.	Heavy	+	66 d	50 and 100 R.U.	+	+		+	0
5	7 mo.	Mod.	+	54 d	50 R.U.	+			+	0
6	15 mo.	Heavy	+	68 d	50 and 100 R.U.	+	+		+	0
8	10 mo.	Heavy	+	50 d	50 R.U.	+			+	Pain

Occasionally enlargement of the breasts, hyperemia and hypertrophy of the vulva and uterine spotting occur. Such findings undoubtedly cause grave concern to the parents, no matter how beneficial the treatment.

The retail cost of the hormone, approximately one dollar per cubic centimeter, limits the private practice of this condition, especially when the course of treatment extends two to three months.

It is with great regret that we cannot substantiate Lewis' claims for this method of therapy. We do, however, anticipate other reports confirming the findings noted in this letter.

J. THORNWELL WITHERSPOON, M.A. (OXON) M.D.

Tulane University Medical School
New Orleans, La.

Dear Doctor Kosmak:

In the article entitled "Harmful Effects of Certain Chemical Substances Upon the Uterus of the Rat," by Mr. Kiven and myself (this Journal, vol. 29, No. 4, April, 1935), I regret that I did not quote correctly a reference to an article which appeared in the *Journal of the American Medical Association* of June 11, 1932, page 2155. This is a report of the Bureau of Investigation. In reviewing this article I state that the Bureau has found reports of some 25 fatal cases resulting from the use of "Provocal." (This is the name under which Leunbach paste is sold abroad.) The fact of the matter is that in this report both Provocal and another paste (Interruptin) are discussed and the statement is made that "there have recently appeared in German literature reports of 25 deaths that have resulted from the use of these abortifacient pastes."

In justice to the manufacturers I would ask you to publish this correction.

Yours very truly,

(Signed) FRED E. D'AMOUR.

Denver, Colorado.
May 6, 1935.

Hulpieu, Weatherby, and Culbertson: A Comparative Study of the Kelly Test and the Friedman Modification of the Zondek-Aschheim Test for Pregnancy, J. Lab. & Clin. Med. **20:** 63, 1934.

The Kelly pregnancy test depends upon the fact that urine from pregnant women will cause the premature opening of the vaginal orifice of immature rats. The technic, slightly modified by these authors, consists in the intraperitoneal injection of 2.5 c.c. of urine, twice on successive days. The final examination of the rats is made at the end of ninety-six hours. The urine is rendered neutral to litmus, filtered and warmed approximately to body temperature before injection. Catheterized specimens are used in most instances.

In this series a total of 59 cases were studied. Friedman tests were also carried out from the same urine specimens. By checking with the subsequent histories of the patients there were 19 cases of pregnancy and 40 with no pregnancy. The Friedman test showed 20 positives and the Kelly test 21 positives. The error in the Friedman test was due to retention of part of the placenta after an abortion; the Kelly test showed this same error. The other error in the Kelly test occurred in the case of an ovarian cyst; the Friedman test on this case was negative.

The Friedman test depends upon the presence of an anterior pituitary hormone in pregnancy urine, while the Kelly test depends upon increased secretion of female sex hormone by the rat as a result of the stimulation of its ovaries by anterior pituitary hormone found in pregnancy urine. In certain pathologic conditions of nonpregnant women, sufficient female sex hormone may be excreted in the urine to produce a premature opening of the vaginal orifice in the rat, and thus give a false positive Kelly test as in the ovarian cyst case.

There were thirty-eight negative results from the Friedman test which were correct; one animal died. There were twenty-nine negative results from the Kelly test which were correct, and nine rats died. The earliest positive test was obtained one month after the last period, and another was positive approximately six weeks after the last period. The Kelly test has several advantages when compared with the Friedman test, viz: ease of handling animals, economy, and it is not necessary to kill or operate on the test animal. The disadvantages are: approximately double the time is required, certain pathologic conditions in which a large amount of female sex hormone is excreted in the urine may give false positive results, and the mortality rate among the rats is likely to be high as a result of intraperitoneal injections.

W. B. SERBIN.

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